Betapol®

Closer to nature every day

Scientific summary

BUNGE
Loders Croklaan

Summary

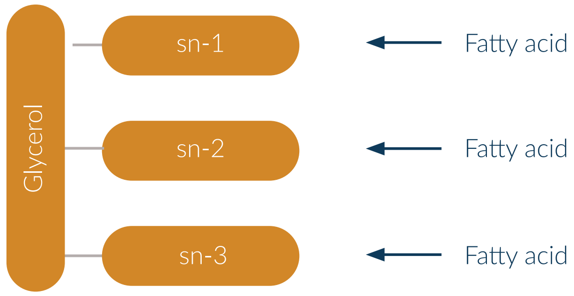
Human breast milk supplies vital nutrients to infants and is the gold standard to which all infant formulas are compared. While many infant formulas supply necessary nutrients comparable to breast milk, the type of fat can differ significantly. Human breast milk fat largely contains a unique placement of palmitic acid on the sn-2 position of the triglyceride and although infant formulas can contain palmitic acid, the placement of palmitic acid at the sn-2 position is much lower. High sn-2 palmitic acid is the same triglyceride structure found in human milk fat and serves as a functional ingredient when added to infant formulas. Studies show that high sn-2 infant formula (high sn-2 IF), much like breast milk, leads to increased fatty acid absorption, increased calcium absorption, reduced formation of fecal calcium soaps, and softer stools vs. fat sources used in common commercial infant formulas.

Introduction

For exclusively breastfed infants, human breast milk is the sole source of nutrients during the first several months. As human breast milk supplies all the nutrients required for growth, development and immune support, it is often considered the gold standard in infant nutrition.
Breastfeeding is not always practiced and commercial infant formulas exist which can serve as suitable substitutes.
Over the years, infant formulas have become more sophisticated regarding nutrient additions which naturally appear in human breast milk and include prebiotic oligosaccharides, nucleotides, carotenoids and probiotic bacteria. However, there is one key ingredient which appears in human breast milk that has not been widely applied to infant formula and that is the distinctive fat structure.
The fat structure in human breast milk is unique and serves a functional purpose (1,2). Human breast milk is made up of only about 3-4% fat; however, the fats make up 50-60% percent of the energy intake for infants and are involved in nutrient absorption (1). Thus, the fat in human breast milk plays an essential role in infant nutrition and digestion.
In nature, fat molecules exist as fork-shaped triglycerides which can have different fatty acids bound to the sn-1, sn-2, or sn-3 position on a glycerol backbone (Figure 1).

Key words:
Infant formula, Fat, Human breast milk, Palmitic acid, Structured triglycerides, Calcium absorption, Stools

Figure 1 Triglyceride structure with three fatty acids attached.



sn-1 and sn-3 are the outer fatty acid positions and sn-2 the mid-position fatty acid. (sn means stereospecific numbering)

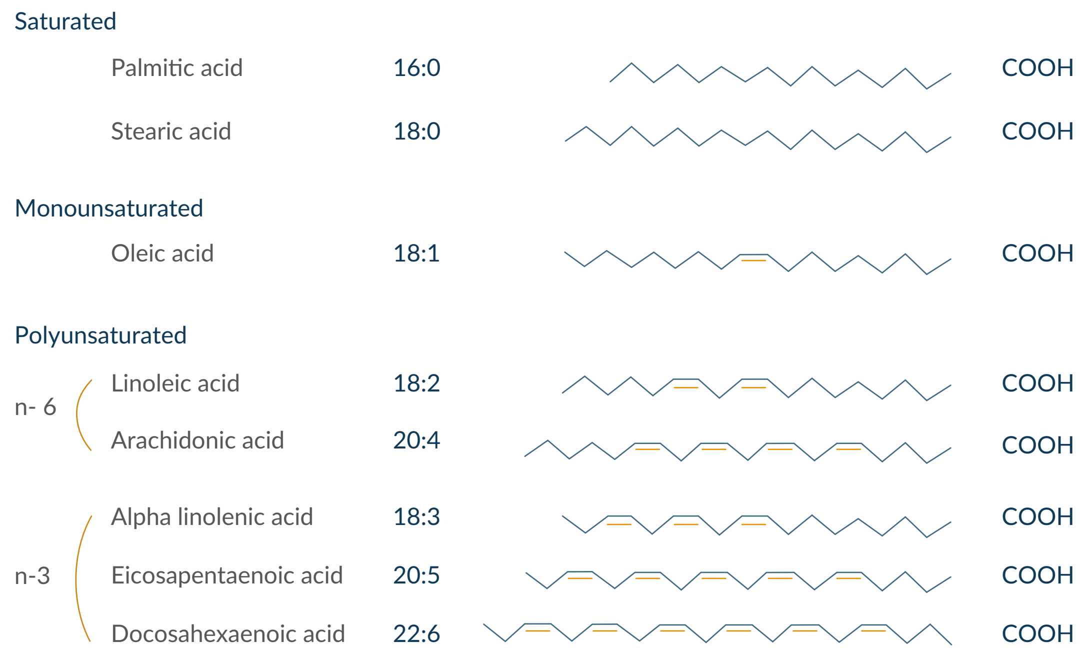
The OPO fat structure allows babies to absorb more palmitic acid and calcium

Fatty acids are classified into one of three types, called saturated fatty acids, mono unsaturated fatty acids (MUFA), or polyunsaturated fatty acids (PUFA). Fatty acids can vary in chain lengths from short (<C:6) medium(C:6-C:12) or long (C:12-C:20) or very long (C:22) (Figure 2).

Human breast milk contains various fatty acids, including palmitic acid (C16:0) which makes up 20-25% of the total fatty acids (2). In human breast milk, palmitic acid largely exists (about 70%) on the sn-2 (or middle) position whereas the sn-1 and sn-3 positions are commonly occupied by unsaturated fatty acids such as oleic (18:1) and linoleic (18:2) (3). A similar fatty acid profile to human breast milk can be achieved in infant formulas via the use of vegetable oils and algal oils. However, the specific placement of palmitic acid on the triglyceride in human breast milk differs from most infant formulas and cannot be matched by the addition of vegetable oils. While palmitic acid exist primarily in the sn-2 position in human milk fat, in most infant formula palmitic acid exists largely (about 80%) in either the sn-1 or sn-3 position (3). This difference in palmitic acid placement on the triglyceride plays a crucial role in the uptake, digestion, and metabolism of milk fat for infants (4).

Betapol® (high sn-2 Infant Formula (IF)) from Bunge Loders Croklaan is a structured triglyceride mixture derived from vegetable oils and that is identical to the structure of the major triglyceride found in human breast milk.
It is manufactured by using position-specific enzymatic interesterification process using palm oil triglycerides and oleic acid fatty acids. Unlike common triglycerides found in most infant formulas, high sn-2 IF is more like human milk fat and has up to 60% of its palmitic acid attached to the sn-2 position with sn-1 and sn-3 positions occupied by unsaturated fatty acids. Studies have shown that the addition of high sn-2 IF as the fat source of an infant formula can play a beneficial role in lipid absorption, energy availability, mineral absorption and stool softness in both preterm and term infants vs. commercial formulas that contain low levels of sn-2 palmitic acid (4-9).
In addition, novel infant formulas which contain high sn-2 IF and other ingredients naturally found in human breast milk such as oligosaccharides have shown benefits such as softer stools, alleviation of constipation and increased probiotic bifidobacteria in the gut (10-14). Table 1 summarizes efficacy of high sn-2 IF research.

Figure 2 Different types of dietary fatty acids.

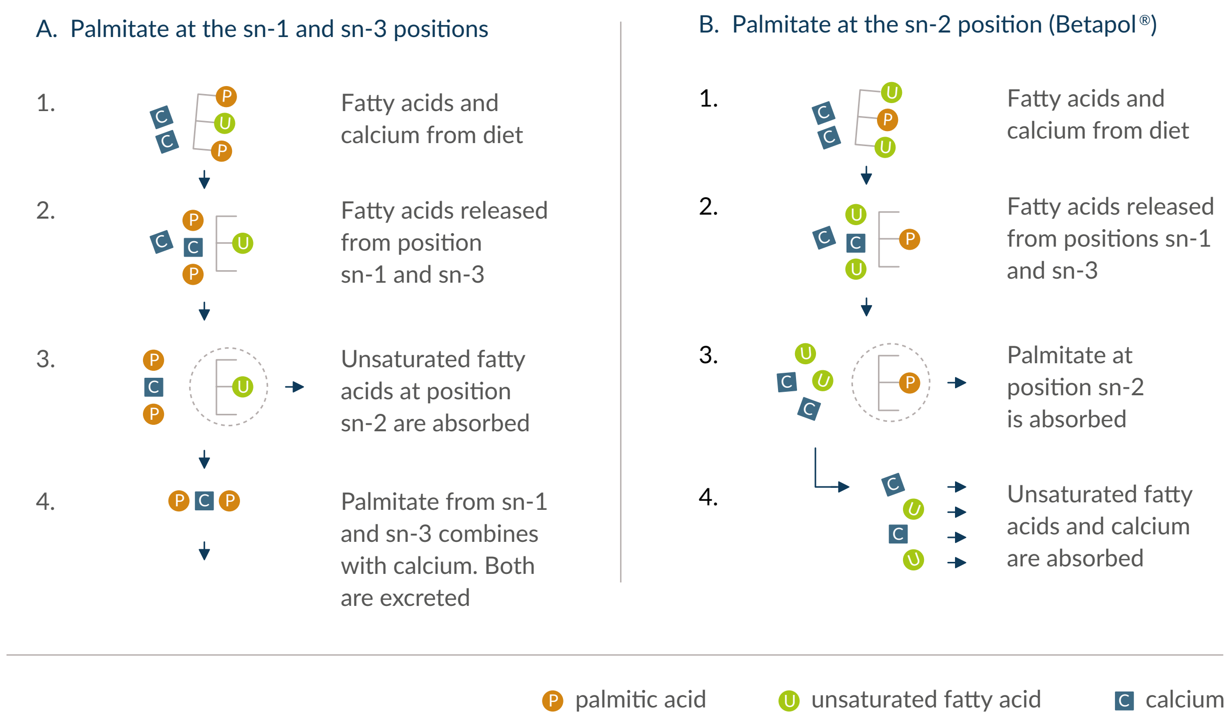


High sn-2 IF increases lipid absorption

Lipid absorption is essential for the energy requirements of the growing infant. In addition, some lipids found in breast milk such as DHA, EPA and rumenic acid also serve roles in other key biological functions such as cognition and immune function (15-17). The rate of lipid absorption is influenced by both the type of fatty acid and the position of fatty acid on the triglyceride backbone (3). When triglycerides are consumed, the fats bound in the sn-1 and sn-3 positions are freed by digestive enzymes leaving the fatty acid in the sn-2 position as a monoglyceride where each can be absorbed in the small intestine.

Generally, short or medium chain fatty acids are more quickly absorbed than long chain fatty acids and unsaturated fatty acids are better absorbed than saturated fatty acids (3,18). Palmitic acid is favorably absorbed in the sn-2 position as a monoglyceride rather than a free fatty acid from the sn-1 or sn-3 position (19-21). Free palmitic acid tends to complex with minerals such as calcium and form insoluble soaps which cannot be absorbed in the small intestine and are thus excreted in the feces (1,22) as illustrated in Figure 3.

Figure 3 Lipid digestion and fatty acid absorption pathways.



When palmitic acid exist in the sn-1 and sn-3 position (A.) they can bind with minerals after digestion and reduce absorption. When palmitic acid exists in the sn-2 position (B), it does not bind with minerals and is more readily absorbed.

Table 1 Summary of clinical studies performed on high sn-2 IF or high sn-2 IF with a combination of ingredients. (1/2)

Reference	No. infants	Duration	Intervention IF	Control IF	Outcomes
Carnielli 1995	24 (preterm) up to 38 days of age	1 week crossover	58% sn-2 palmitic acid	9.8% sn-2 palmitic acid	28% decrease in fecal calcium (p<0.05) Significant increase in intestinal absorption of myristic, palmitic and stearic acid (p<0.01) Significant decrease in fecal myristic, palmitic and stearic acid content (p<0.004)
Carnielli 1996	27 (term) male infants up to 5 weeks of age	5 weeks	66% (Beta) and 47% (Intermediate) sn-2 palmitic acid	13% (regular) sn-2 palmitic acid	Significant decrease in fecal calcium and significant increase in intestinal calcium absorption with the Beta formula. Significant decrease in fat excretion with Beta formula (p<0.001) Significant decrease in fecal lauric, myristic, palmitic and stearic acid content (p<0.001) with the Beta formula Significant difference in stool consistency (p=0.03)
Lucas 1997	24 (preterm) up to 10 days of age	3 weeks	74% (Betapol®) and 28% (Diet B) sn-2 palmitic acid	8% (Diet A) sn-2 palmitic acid	Significant increase in calcium absorption with high sn-2 IF (p<0.03) Significantly less fecal fatty acid soaps with high sn-2 IF (p<0.03) Significant increase in palmitic acid absorbed with high sn-2 IF (p<0.03)
Kennedy 1999	203 (term) up to 8 days of age	12 weeks	50% (Betapol®) sn-2 palmitic acid	12% (Control) sn-2 palmitic acid	Significant increase in BMC (p<0.02) and BMD with high sn-2 IF (p<0.009) Significantly lower soap fatty acids (p<0.001) and total fatty acids in feces (p<0.05) with high sn-2 IF significantly less hard or formed stools at six weeks with high sn-2 IF (p<0.004)
Lopez-Lopez 2001	36 (term) from birth	8 weeks	Breast fed (66% sn-2 palmitic acid) Beta formula (44% sn-2 palmitic acid)	Alpha formula19% (control) sn-2 palmitic acid	Significantly less fecal palmitic acid in the breastfed and beta formula groups Significantly less fecal calcium in breast fed group vs. alpha and beta formula
Bongers 2007	38 (term) constipated infants up to 29 weeks in age	3 week crossover	41% sn-2 palmitic acid contains oligosaccharides and whey hydrolyzed protein (new formula)	11.5% sn-2 palmitic acid, no oligosaccharides, no hydrolyzed whey protein (standard formula)	Significant improvement in stool consistency for new formula (p=0.04)
Savino 2005	168 (term) infants with regurgitation of constipation problems up to four months of age	14 days	High sn-2 IF, prebiotic oligosaccharides and partially hydrolyzed whey protein	Listed as standard IF	Increased stool frequency on day 7 (0.48, p=0.02) and day 14 (0.40, p=0.07)

Table 1 Summary of clinical studies performed on high sn-2 IF or high sn-2 IF with a combination of ingredients. (2/2)

Reference	No. infants	Duration	Intervention IF	Control IF	Outcomes
Savino 2003	232 infants with constipation up to 90 days of age	14 days	High sn-2 IF, prebiotic oligosaccharides and partially hydrolyzed whey protein	None	141 (of 201) infants (70%) had less regurgitation symptoms at the end of the study (p<0.005). 147 (of 232) infants (63%) demonstrated an increase in daily stool number (0.42, p<0.05). Stool frequency was increased from day 1 to day 7 (0.41, p<0.05).
Savino 2006	199 infants with infantile colic age up to four months of age	14 days	High sn-2 IF, prebiotic oligosaccharides and partially hydrolyzed whey protein	Listed as standard formula and simethicone	Colic episode were less after 1 week (p<0.001) and crying episodes were less after 2 weeks (p<0.001)
Yao 2014	300 term infants (7-14 days old)	8 weeks	36-37% sn-2 palmitate (Betapol®), with or w/o oligofructose (OF) sn-2, sn-2+3 g/L OF, or sn-2+5 g/L OF	11.7% sn-2 palmitate (standard) and human milk fed infants	Sn-2 vs. control with standard formula, decreased stool soap palmitate (46% less, P<0.001) and softer stools (20% more mushy soft stools, P=0.026; 50% fewer formed stools, P=0.003). Addition of OF resulted in even fewer formed stools versus control, with 5 g/L OF more closely resembling that of HM-fed infants. Both sn-2 (P<0.05) and sn-2 with OF groups (P<0.01) had significantly higher fecal bifidobacteria concentrations than control at week 8, not differing from HM-fed infants.
Schmelzle 2003	102 healthy full term infants	12 weeks	High sn-2 IF with oligosaccharides and hydrolyzed protein (new formula)	Control formula	At six weeks, new formula produced softer stool (p=0.005) and produced higher counts of probiotic Bifidobacteria (p<0.005) than the control formula.
Wu 2021	199 healthy full term infants	24 weeks	46.3% sn-2 palmitate formula with Betapol® (sn-2 group); Breastfed group	10.3% sn-2 palmitate formula (control group);	At week 16, the sn-2 group showed significantly lower risk of scoring close to the normal development threshold for fine motor skills compared to the control group (p=0.036), and did not differ from the breastfed group (p=0.513). At weeks 16 and 24, the sn-2 group had significantly higher relative abundance of fecal Bifidobacteria than the control group (week 16: p=0.001, week 24: p=0.028) and did not differ from the breastfed group (week 16: p=0.674, week 24: p=0.749).

Long-term research program to identify and substantiate new Betapol® benefits

The presence of fecal palmitic acid represents a needless loss of available dietary energy for the infant. Effects of improved lipid absorption by high sn-2 IF have been shown in preterm term infants where nutrient absorption is paramount as they have a less developed digestion systems vs. full term infants (2,23,24).

A five-day study in 24 preterm infants compared the lipid absorption of high sn-2 IF (73% palmitic acid in the sn-2 position) vs. two other triglycerides with only 28% or 8% of palmitic acids in the sn-2 positions (4). The study found that 91% of the palmitic acid was absorbed from high sn-2 IF vs. 79% of the palmitic acid from the other two triglycerides (p<0.01).

A similar 1-week crossover trial in 12 preterm infants (born after gestation of 20-32 weeks) using infant formula with high sn-2 IF vs. control infant formula (with only 13% of palmitic acid in the sn-2 position) found significantly greater intestinal absorption of the saturated fatty acids palmitic (43.1%), myristic (12.5%), and stearic (6.7-fold increase) with high sn-2 IF with respect to the commercial infant formula (p<0.01) (5).

The effects of high sn-2 IF on lipid absorption have also been shown in full term infants. A five-week study in full term infants compared infant formula containing high sn-2 IF (up to 60% palmitic acid in the sn-2 position) to a conventional infant formula (13% palmitic acid in the sn-2 position) and also to an intermediate formula (39% of palmitic acid in the sn-2 position) (6). The infant intestinal absorption of saturated fatty acids lauric (25.4%), myristic (7.6-fold), palmitic (23.5%) and stearic (20.7%) acids was significantly greater (p<0.01) after consumption of high sn-2 IF vs. the standard and intermediate formulas. The amount of fatty acids recovered in feces was significantly lower in the formula containing high sn-2 IF (150 mg/kg/day) vs. the conventional (680 mg/kg/day, p<0.05) and intermediate formulas (440 mg/kg/day, NS).

Another study was performed in 36 term infants consuming human breast milk for two months (Group A, 66% sn-2 palmitic acid estimated), conventional infant formula for two months (Group B, 19% sn-2 palmitic acid), and Group C which was fed the formula from Group B for one month and then a high sn-2 IF (44.5% sn-2 palmitic acid) for the second month (9). After two months, the authors reported significantly less fecal palmitic acid in Groups A and C (which had larger amounts on sn-2 palmitic acid for either one or two months) than Group B, indicative of increased palmitic acid absorption.

High sn-2 IF triglyceride structure significantly increases absorption of fatty acids and leads to a lower amount of excreted fatty acids in both preterm and term infants vs. triglycerides with low sn-2 palmitic acid found in common infant formulas.

High sn-2 IF increases calcium absorption

Calcium absorption is important as calcium is a vital mineral involved in bone building and also serving as a cellular signal in several biological processes. When saturated fatty acids are bound to the sn-1 and sn-3 positions on a triglyceride, they can be released to form free fatty acids during digestion. These free fatty acids can bind to minerals such as calcium to form soaps which are excreted in feces thus decreasing the amount of calcium available for absorption for the infant. Indeed, fecal calcium content is positively correlated with fecal saturated fatty acid content in infants and not mono or polyunsaturated fatty acids (5). A study in preterm infants consuming infant formula with high sn-2 found that fecal calcium was significantly lower (58.8 mg/kg/day) in the high sn-2 IF containing infant formula vs. the control formula (82.0 mg/kg/day) ($p<0.05$) (5). Another study in preterm infants comparing formula containing high sn-2 IF (72% sn-2 palmitic acid) with formulas containing only 8% (formula A) and 28% (formula B) palmitic acid in the sn-2 position respectively found a higher absorption of dietary calcium in the high sn-2 IF (57%) vs. the A and B formulas (44% and 40% respectively) ($p<0.03$) (4). Also found was a significantly lower amount of fecal calcium soaps for the high sn-2 IF (3.3%) vs. the B formula (7.2%) ($p<0.03$).

Similar effects on calcium absorption with high sn-2 IF have been observed in term infants. In a study of full term infants consuming infant formula containing high sn-2 IF had significantly lower amounts of fecal calcium (43mg/kg/day) and significantly higher calcium absorption (53%) vs. a conventional infant formula (68mg/kg/day; 33% absorption) ($p<0.05$) (6).

Another study was performed in 36 term infants (12 infants per group), which compared the effects of breast milk and two other infant formulas with different sn-2 palmitic acid percentages for two months (9). The breast milk contained approximately 66% sn-2 palmitic acid (Group A) and the two other groups consumed conventional infant formula (Group B, 19% sn-2 palmitic acid), and Group C which was fed the formula from Group B for one month and then a higher palmitic acid sn-2 formula (44.5% sn-2 palmitic acid) for the second month. After 1 month, there was a significant difference in fecal calcium in the breast fed group vs. Group B (0.42 mg/100g vs. 1.27 mg/100g). After two months there was a significant difference in fecal calcium in the breast fed group vs. Group B and Group C, (0.23 mg/100g vs. 1.22 mg/100g and 1.01mg/100g).

Calcium absorption in infants is especially important due to its critical role in bone formation and development. The increased calcium absorption of high sn-2 IF leads to improved bone development. A study in 323 infants fed a formula containing high sn-2 IF, a conventional infant formula with sn-2 palmitic acid or breast fed found that there was a 5% increase in both bone mineral density (BMD) ($p<0.009$) and bone mineral content (BMC) ($p<0.02$) in the high sn-2 IF fed infants vs. the conventionally fed infants (7). The BMD and BMC in the high sn-2 IF fed group was similar to the breast fed group.

High sn-2 IF improves fine motor skills

Fine motor skills are broadly interpreted as small muscle movements requiring eye-hand coordination, which could be categorized into subskills such as reaching, grasping, grabbing, holding, and manipulating (30). They are essential in early learning and have long been recognized as an important foundation for development in other domains (31). Fine motor skills could be evaluated through the Ages and Stages Questionnaires Edition 3 (ASQ-3), which is a vital monitoring tool in screening for developmental delays in children younger than 5.5 years old (32).

A study was performed in 199 healthy infants in China, which compared the effects of breast milk (BF group) and two infant formulas for 24 weeks. The two infant formulas were comparable, with the exception that one contained high, 46.3%, sn-2 palmitate (sn-2 group) and the other had low, 10.3%, sn-2 palmitate (control group). The sn-2 palmitate in the high sn-2 palmitate IF was increased by adding Betapol B-55 produced by Bunge Loders Croklaan. After adjusting for maternal education level, infants in the sn-2 group showed significantly lower risk of scoring close to ASQ-3 threshold scores for fine motor skills in similar-aged infants ($p=0.036$). The sn-2 group did not differ significantly from the BF group ($p=0.513$). At week 16 and 24, the sn-2 group had a significantly higher relative abundance of fecal Bifidobateria than the control group ($p=0.001$ and $p=0.028$, respectively), and did not differ from the BF group ($p=0.674$ and $p=0.749$, respectively). In conclusion, increased sn-2 palmitate level in the formula proved to improve infants' development of fine motor skills, and its effect on infant neurodevelopment was associated with increased gut Bifidobacteria level (29).

Stool softness

When saturated fatty acids in the sn-1 or sn-3 position are freed during digestion and bind with minerals, not only does this reduce the amount of available minerals such as calcium, but the resultant fatty acid-calcium soaps accumulate in the feces resulting in harder stools which may lead to constipation or obstruction. Breastfed infants typically have lower amounts of fecal calcium soaps and softer stools than formula fed infants. Quinlan et al (8) visually tested stools from 30 infants and found breast fed infants to have softer stools than formula fed infants. More analytically, they further found that formula fed infants had approximately 9 times the amount of fatty acid calcium soaps in the feces vs. breast fed infants. This amount of calcium soaps in the formula fed infants accounted for nearly 30% of the dry weight of the stool vs. only 3% for the breast fed group. High sn-2 IF is similar to breast milk regarding effects on infant stool softness.

A study using infant formula containing high sn-2 (66% sn-2 palmitic acid) on term infants found significantly softer stools by a subjective scoring method based on photographs using four levels of consistency compared with a conventional infant formula with 13% sn-2 palmitic acids(6) ($p=0.03$). The degree of stool softness observed in this study was independent of water content and directly proportional to the amounts of fatty acid soaps in the stool. Another study showed the stool softness and proportion of fatty acid soaps of infants at 6 and 12 weeks consuming high sn-2 IF to be similar to breast fed infants (7). At 6 weeks the percentage of hard or formed stools was significantly less ($p=0.004$) than a typical conventional infant formula. Stool hardness can lead to pain and discomfort, constipation, and potential further health problems for the infant. High sn-2 IF has been shown to reduce the amount of fatty acid soaps excreted in the feces and lead to softer stools similar to breast fed infants.

Efficacy of high sn-2 IF in combination with other ingredients

Infant formula manufacturers endeavor to discover and include more ingredients into infant formula which are naturally found in breast milk. One example is oligosaccharides which are non-digestible carbohydrates that appear naturally in breast milk and when added to infant formula have been shown to soften stool, increase numbers of probiotic bacteria and may also have some immune benefits as well (10-14,25). Thus, the inclusion of both high sn-2 IF and oligosaccharides in infant formulas yields a closer match to human breast milk.

Studies have been performed in infants using a combination of high sn-2 IF, oligosaccharides and other ingredients. An infant formula containing fructo and galacto-oligosaccharides, partially hydrolyzed whey proteins, low levels of lactose and high sn-2 IF was used in a study to reduce constipation in 232 infants for fourteen days (10). After seven days, 147 infants (63%) demonstrated a significant increase in the daily number of stools (p<0.05).

In a similar study, 168 full term infants with digestive problems such as constipation were fed an infant formula containing high sn-2 IF, prebiotic oligosaccharides and partially hydrolyzed whey protein (11). A standard infant formula was used as a control. Stool consistency and frequency were measured on days 1, 7 and 14 of the study. On day seven, infants on the high sn-2 IF / oligosaccharide/ partially hydrolyzed whey formula had a higher number of evacuations vs. the standard formula (day 1-1.79 vs. 1.31, p=0.02). The difference between the two groups in the number of evacuations from the beginning of the study until day 7 and day 14 was 0.60 (p=0.004) and 0.53 (p=0.015) per day respectively.

A study used a combination of high sn-2 IF, prebiotic oligosaccharides and partially hydrolyzed whey protein evaluated the effects on term infants with constipation vs. a conventional infant formula (12). The study consisted of 38 constipated infants aged 3-20 weeks and randomized to the high sn-2 IF / oligosaccharides formula or the standard formula. After three weeks, defecation frequency increased greater in the high sn-2 IF / oligosaccharides group from 3.5 defecations per week to 5.6 defecations per week post treatment vs. the standard infant formula group which increased from 3.6 defecations per week to 4.9 defecations per week post treatment. Improvement of hard stools to soft stools was found more in the high sn-2 IF / oligosaccharides group (90%) vs. the standard infant formula group (50%) but did not reach statistical significance. However a significant improvement of stool consistency was noted for the high sn-2 IF/oligosaccharide group (p=0.04). In addition, a two-week study using this same formula to measure comfort in infants less than 4 months old found decreases in colic (at 1 week, p<0.001) and crying episodes (after 2 weeks, p<0.001) in 199 infants with infantile colic compared to a standard (low sn-2 palmitic acid) infant formula (13).

Another study found further benefits of the combination of high sn-2 IF with oligosaccharides. In a clinical trial in 102 healthy full term infants for twelve weeks, stool softness and probiotic bifidobacteria growth was measured in an infant formula containing high sn-2, oligosaccharides and hydrolyzed protein vs. control formula. At six weeks, the formula with high sn-2 IF, oligosaccharides and hydrolyzed protein produced softer stool (p=0.005) and produced higher counts of probiotic bifidobacteria (p<0.005) than the control formula (14). Bifidobacterium are non pathogenic bacteria and are major inhabitants of the intestine which may aid in digestion and benefit the immune system (26).

Study with high sn-2 palmitate formulas showed reduced stool soaps, softer stools, and increased bifidobacteria, whereas addition of oligofructose (OF) further improved stool consistency (27). In total 300 healthy term formula-fed infants at 7-14 days old, were fed with standard formula, human milk, sn-2, sn-2+3g/L oligofructose (OF). Sn-2+5g/L OF for 8 weeks (n=75 each group). The sn-2 group had 46% less stool soap palmitate (P<0.001) and softer stools than control (20% more mushy soft stools, P=0.026; 50% fewer formed stools, P=0.003). Addition of OF resulted in even fewer formed stools versus control (65% fewer for sn-2+3 g/L OF, 79% fewer for sn-2+5 g/L OF), with 5 g/L OF more closely resembling that of HM-fed infants. Both sn-2 (P<0.05) and sn-2 with OF groups (P<0.01) had significantly higher fecal bifidobacteria concentrations than control at week 8, not differing from HM-fed infants (27).

Although the IF in the above mentioned studies were efficacious for various endpoints, the objective of each of these studies was not to determine the efficacy of individual ingredients. Nonetheless, these studies suggest that adding components which appear in breast milk such as high sn-2 fat and oligosaccharides can be beneficial for the infants vs. IF which do not contain them.

Conclusion

In conclusion, breast milk supplies vital nutrients to infants and is the gold standard to which all infant formulas are compared. While many infant formulas supply necessary nutrients comparable to breast milk, the type of fat can differ significantly. Although infant formulas can contain palmitic acid, the unique placement of palmitic acid on the sn-2 position of the triglyceride in breast milk is not representative of most infant formulas. High sn-2 palmitic acid is the same triglyceride structure found in human milk fat and serves as a functional ingredient when added to infant formulas. Studies show that high sn-2 IF, much like breast milk, leads to increased fatty acid absorption, increased calcium absorption, increased BMC and BMD, reduced formation of fecal calcium soaps, and softer stools vs. fat sources which contain palmitic acid used in common commercial infant formulas. As infant formula manufactures continue to add novel ingredients to infant formulas to make them closer to human breast milk, it is vital to also include the same type of fat that is found naturally in breast milk, which is high sn-2 palmitic acid. The noted beneficial effects on nutrient absorption, softer stools, reduced constipation and probiotic bacteria from high sn-2 IF along with other ingredients found in breast milk can lead to a healthier and happy infant. No infant formula is superior to breast milk, however the nutritional similarities of high sn-2 IF to human milk fat shown vs. other types of triglycerides demonstrates the importance of high sn-2 IF to be included in all infant formulas.

References

1 **Jensen C, Buist NR, Wilson T (1986)** Absorption of individual fatty acids from long chain or medium chain triglycerides in very small infants Am J Clin Nutr 43(5) 745-51.

2 **Breckenridge WC, Marai L, Kuksis A (1969)** Triglyceride structure of human milk fat Can J Biochem 47(8)761-9

3 **Bracco U (1994)** Effect of triglyceride structure on fat absorption Am J Clin Nutr 60 (6 Suppl) 1002S-1009S

4 **Lucas A, Quinlan P, Abrams S, Ryan S, Meah S, Lucas PJ (1997)** Randomised controlled trial of a synthetic triglyceride milk formula for preterm infants Arch Dis Child Fetal Neonatal Ed 1997 77(3) F178-84

5 **Carnielli VP, Luijendijk IH, van Goudoever JB, Sulkers EJ, Boerlage AA et al (1995)** Feeding premature newborn infants palmitic acid in amounts and stereoisomeric position similar to that of human milk: effects on fat and mineral balance Am J Clin Nutr 61(5) 1037-1042

6 **Carnielli VP, Luijendijk IH, Van Goudoever JB, Sulkers EJ, Boerlage AA, Degenhart HJ, Sauer PJ (1996)** Structural position and amount of palmitic acid in infant formulas: effects on fat, fatty acid, and mineral balance J Pediatr Gastroenterol Nutr 23(5) 553-60

7 **Kennedy K, Fewtrell MS, Morley R, Abbott R, Quinlan PT, Wells JC, Bindels JG, Lucas A (1999)** Double-blind, randomized trial of a synthetic triacylglycerol in formula-fed term infants: effects on stool biochemistry, stool characteristics, and bone mineralization Am J Clin Nutr 70(5) 920-27

8 **Quinlan PT, Lockton S, Irwin J, Lucas AL (1995)** The relationship between stool hardness and stool composition in breast- and formula-fed infants J Pediatr Gastroenterol Nutr 20(1) 81-90

9 **López-López A, Castellote-Bargalló AI, Campoy-Folgoso C, Rivero-Urgël M, Tormo-Carnicé R, Infante-Pina D, López-Sabater MC (2001)** The influence of dietary palmitic acid triacylglyceride position on the fatty acid, calcium and magnesium contents of at term newborn faeces Early Hum Dev. 65 Suppl S83-94

10 **Savino F, Cresi F, Maccario S, Cavallo F, Dalmasso P, Fanaro S, Oggero R, Vigi V, Silvestro L (2003)** “Minor” feeding problems during the first months of life: effect of a partially hydrolysed milk formula containing fructo- and galacto-oligosaccharides Acta Paediatr Suppl 91(441) 86-90

11 **Savino F, Maccario S, Castagno E, Cresi F, Cavallo F, Dalmasso P, Fanaro S, Oggero R, Silvestro L (2005)** Advances in the management of digestive problems during the first months of life Acta Paediatr Suppl 94(449) 120-124

12 **Bongers ME, de Lorijn F, Reitsma JB, Groeneweg M, Taminiau JA, Benninga MA (2007)** The clinical effect of a new infant formula in term infants with constipation: a double-blind, randomized cross-over trial Nutr J 6 (8)

13 **Savino F, Palumeri E, Castagno E, Cresi F, Dalmasso P, Cavallo F, Oggero R (2006)** Reduction of crying episodes owing to infantile colic: A randomized controlled study on the efficacy of a new infant formula. Eur J Clin Nutr 60(11) 1304-1310

14 **Schmelzle H, Wirth S, Skopnik H, Radke M, Knol J, Böckler HM, Brönstrup A, Wells J, Fusch C (2003)** Randomized double-blind study of the nutritional efficacy and bifidogenicity of a new infant formula containing partially hydrolyzed protein, a high beta-palmitic acid level, and nondigestible oligosaccharides. J Pediatr Gastroenterol Nutr 36(3) 343-351

15 **Judge MP, Harel O, Lammi-Keefe CJ (2007)** Maternal consumption of a docosahexaenoic acid-containing functional food during pregnancy: benefit for infant performance on problem-solving but not on recognition memory tasks at age 9 mo Am J Clin Nutr 85(6) 1572-1577

16 **Ryan AS, Astwood JD, Gautier S, Kuratko CN, Nelson EB, Salem N Jr (2010)** Effects of long-chain polyunsaturated fatty acid supplementation on neurodevelopment in childhood: A review of human studies Prostaglandins Leukot Essent Fatty Acids 82(4-6) 305-314

17 **Ramírez-Santana C, Castellote C, Castell M, Rivero M, Rodríguez-Palmero M, Franch A, Pérez-Cano FJ (2009)** Long-term feeding of the cis-9,trans-11 isomer of conjugated linoleic acid reinforces the specific immune response in rats J Nutr 139(1) 76-81

18 **Mu H, Høy CE (2001)** Intestinal absorption of specific structured triacylglycerols J Lipid Res 42(5) 792-798

19 **Tomarelli RM, Meyer BJ, Weaber JR, Bernhart FW (1968)** Effect of positional distribution on the absorption of the fatty acids of human milk and infant formulas. J Nutr (95) 583-590

20 **Filer LJ Jr, Mattson FH, Fomon SJ (1969)** Triglyceride configuration and fat absorption by the human infant J Nutr 99(3) 293-298

21 **Quinlan, P.** Structuring fats for incorporation into infant formulas in Fat in the diet. Proceedings of the 21st World Congress of the International Society for Fat Research. (ISF), October 1995; The Hague, Netherlands. PJ Barnes & Associates Bridgewater, UK 1996, p. 21 Abstract.

22 **Bosworth AW, Bowditch HI, Giblin LA (1918)** Studies of infant feeding X. Calcium in its relation to the absorption of fatty acids. Am J Dis Child (15) 397-407

23 **Martin JC, Bougnoux P, Antoine IM. Lanson M, Couet E (1993)** Triacylglycerol structure of human colostrum and mature milk. Lipids (28) 637-43.

24 **Pitas RE, Sampugna J, Jensen RG (1967)** Triglyceride structure of cow’s milk fat. I Preliminary observations on the fatty acid compositions of positions 1,2 and 3 J Dairy Sci (50) 1332-1336.

25 **van Hoffen E, Ruiter B, Faber J, M’Rabet L, Knol EF, Stahl B, Arslanoglu S, Moro G, Boehm G, Garssen J (2009)** A specific mixture of short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides induces a beneficial immuno-globulin profile in infants at high risk for allergy Allergy 64(3) 484-487.

26 **Kleerebezem M, Vaughan EE (2009)** Probiotic and gut lactobacilli and bifidobacteria: molecular approaches to study diversity and activity Annu Rev Microbiol (63) 269-290 Review

27 **Yao MJ, Lien EL, Capeding MRZ, Fitzgerald M, Ramanujam K, Yuhas R, Northington R, Lebumfacil J, Wang L and DeRusso PA (2014)** Effects of term infant formulas containing high sn-2 palmitate with and without oligofructose on stool composition, stool characteristics,

28 **Schmelzle H, Wirth S, Skopnik H, Radke M, Knol J, Böckler HM, Brönstrup A, Wells J, Fusch C (2003)** Randomized double-blind study of the nutritional efficacy and bifidogenicity of a new infant formula containing partially hydrolyzed protein, a high beta-palmitic acid level, and nondigestible oligosaccharides. J Pediatr Gastroenterol Nutr 36(3) 343-351 REFERENCES 52772

29 **Wu, W., Zhao, A., Liu, B., Ye, W. H., Su, H. W., Li, J., & Zhang, Y. M. (2021).** Neurodevelopmental Outcomes and Gut Bifidobacteria in Term Infants Fed an Infant Formula Containing high sn-2 Palmitate: A Cluster Randomized Clinical Trial. Nutrients, 13(2), 693.

30 **Martzog, P., & Suggate, S. P. (2019).** Fine motor skills and mental imagery: Is it all in the mind?. Journal of experimental child psychology, 186, 59–72.

31 **Pitchford, N. J., Papini, C., Outhwaite, L. A., & Gulliford, A. (2016).** Fine Motor Skills Predict Maths Ability Better than They Predict Reading Ability in the Early Primary School Years. Frontiers in psychology, 7, 783.

32 **Chong, K. C., Zhou, V. L., Tarazona, D., Tuesta, H., Velásquez-Hurtado, J. E., Sadeghi, R., & Llanos, F. (2017).** ASQ-3 scores are sensitive to small differences in age in a Peruvian infant population. Child: care, health and development, 43(4), 556–565.

Let's create together

BUNGE
Loders Croklaan

bungeloders.com