Palm Oil and Beta-palmitate in Infant Formula: A Position Paper by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Committee on Nutrition

*Jiri Bronsky, †Cristina Campoy, ‡Nicholas Embleton, §Mary Fewtrell, ¶Nataša Fidler Mis, ||Konstantinos Gerasimidis, **Iva Hojsak, ††Jessie Hulst, ‡‡Flavia Indrio, §§¶¶Alexandre Lapillonne, ||||***Christian Molgaard, †††Sissel Jennifer Moltu, ‡‡‡Elvira Verduci, §§§Rakesh Vora, and ¶¶¶Magnus Domellöf, ESPGHAN Committee on Nutrition

ABSTRACT

Background: Palm oil (PO) is used in infant formulas in order to achieve palmitic acid (PA) levels similar to those in human milk. PA in PO is esterified predominantly at the SN-1,3 position of triacylglycerol (TAG), and infant formulas are now available in which a greater proportion of PA is in the SN-2 position (typical configuration in human milk). As there are some concerns about the use of PO, we aimed to review literature on health effects of PO and SN-2-palmitate in infant formulas.

Methods: PubMed and Cochrane Database of Systematic Reviews were systematically searched for relevant studies on possible beneficial effects or harms of either PO or SN-2-palmitate in infant formula on various health outcomes.

Results: We identified 12 relevant studies using PO and 21 studies using SN-2-palmitate. Published studies have variable methodology, subject characteristics, and some are underpowered for the key outcomes. PO is associated with harder stools and SN-2-palmitate use may lead to softer stool consistency. Bone effects seem to be short-lasting. For some outcomes (infant colic, faecal microbiota, lipid metabolism), the number of studies is very limited and summary evidence inconclusive. Growth of infants is not influenced. There are no studies published on the effect on markers of later diseases.

Conclusions: There is insufficient evidence to suggest that PO should be avoided as a source of fat in infant formulas for health reasons. Inclusion of high SN-2-palmitate fat blend in infant formulas may have short-term effects on stool consistency but cannot be considered essential.

Key Words: colic, constipation, growth, lipids, palm olein, palmitic acid

(*JPGN* 2019;68: 742–760)

What Is Known

- Palm oil is used as source of fat in infant formula in order to achieve palmitic acid levels comparable to human milk.
- Palmitic acid in human milk is predominantly at the SN-2 position, in palm oil it is predominantly at the SN-1,3 position. SN-2-palmitate is used in some formulas to mimick palmitic acid position in human milk.

What Is New

- There is insufficient evidence to suggest that palm oil should be avoided as a source of fat in infant formulas for health reasons.
- Inclusion of high SN-2-palmitate fat blend in infant formulas may have short-term effects on stool consistency but cannot be considered essential.

LIPIDS IN HUMAN MILK AND INFANT FORMULAS

Lipids in human milk serve as a major source of energy and essential fatty acids (FA) for the breastfed infants. They also

Received October 22, 2018; accepted February 4, 2019.

From the *Department of Paediatrics, University Hospital Motol, Prague, Czech Republic, the †Department of Paediatrics, University of Granada, Spain, the ‡Newcastle Neonatal Service, Newcastle Hospitals NHS Trust and Newcastle University, Newcastle upon Tyne, UK, the §Childhood Nutrition Research Centre, UCL GOS Institute of Child Health, London, UK, the ¶Department of Gastroenterology, Hepatology and Nutrition, University Children's Hospital, University Medical Centre Ljubljana, Slovenia, the ||Human Nutrition, School of Medicine, Dentistry and Nursing, University of Glasgow, New Lister Building, Glasgow Royal Infirmary, Glasgow, UK, the **Children's Hospital Zagreb, University of Zagreb School of Medicine, Zagreb, Croatia, the ††Department of Paediatric Gastroenterology, Erasmus MC, Sophia Children's Hospital, Rotterdam, The Netherlands, the ‡‡Ospedale Pediatrico Giovanni XXIII University of Bari, Bari, Italy, the §§Paris Descartes University, APHP Necker-Enfants Malades hospital, Paris, France, the ¶¶CNRC, Baylor College of Medicine, Houston, Texas, the ||||Department of Nutrition, Exercise and Sports, University of Copenhagen, the ***Pediatric Nutrition Unit, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark, the †††Department of Neonatal Intensive Care, Oslo University Hospital, Oslo, Norway, the ‡‡‡Department of Pediatrics, San Paolo Hospital, Department of Health Sciences, University of Milan, Milan, Italy, the §§§Leeds teaching hospitals NHS trust, Leeds, UK, and the ¶¶¶Department of Clinical Sciences, Pediatrics, Umeå University, Umeå, Sweden.

Address correspondence and reprint requests to Jiri Bronsky, MD, PhD, Associate Professor of Paediatrics Gastroenterology and Nutrition Unit, Department of Paediatrics, University Hospital Motol, V Uvalu 84, 15006, Prague 5, Czech Republic (e-mail: jiri.bronsky@gmail.com).

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (*www.jpgn.org*).

Secretary of CoN: I.H.; Chair of CoN, M.D.

facilitate absorption of fat-soluble dietary components and support gastrointestinal function, lipid and lipoprotein metabolism, neurodevelopment, and immune function (1,2). Almost 100% of human milk fat is composed by triacylglycerols (TAG). FA in human milk are either saturated (SFA, 35%–40%), monounsaturated (MUFA, 45%–50%), or polyunsaturated (PUFA, approximately 15%) (1,2). Palmitic acid (PA, C16:0) provides the major part of the total SFA content and its concentration is kept relatively constant in breastfeeding mothers (2,3). Human milk TAG are predominantly esterified with PA in the SN-2 position and this configuration facilitates absorption in infants after digestion by human pancreatic lipase that is SN-1,3-specific. Nonesterified FA liberated from the SN-1 and SN-3 positions are quite well absorbed if they are unsaturated because of their water solubility. On the contrary, poorly absorbed saturated FA, such as PA tend to form calcium (Ca) soaps that are excreted in stool and increase stool hardness. However, pancreatic lipolysis of human milk TAG with PA esterified predominantly to the SN-2 position results in formation of water-soluble palmitoyl-monoglycerol. This reduces FA and Ca malabsorption and enables the breastfed infant to benefit from PA as source of fat (see Fig. 1) (1,2,4–10).

The fat in infant formula comes mainly from vegetable oils. Palm oil (PO) is used in order to achieve PA levels similar to those in human milk. Recently, there has been an increasing discussion regarding the use of PO in food products, mostly because of environmental concerns but PO also has potential important health effects. In PO, PA is esterified predominantly at the SN-1,3 position of TAG. As the intestinal absorption of SN-1,3-palmitate is not optimal, there have been attempts to replace it, at least partly, in infant formulas with SN-2-predominant TAG (beta-palmitate), which is the form present in human milk. A number of products using either a mixture of fat or commercial synthetic beta-palmitate (eg, Betapol, INFAT, LipoMilk or Zhejiang Beijia product) in order to achieve high SN-2 content are available on the market. Betapol is produced by interesterifying a tripalmitin-rich PO fraction with a mixture of other fats by using the SN-1,3-specific lipase from *Rhizomucor miehei* (code SP-392; Novo Industries, Copenhagen, Denmark). INFAT (Advanced Lipids, Karlshamn, Sweden) is produced by a patented enzymatic process, which restructures the fat in a way that mimics the structure of PA in human milk (SN-2 predominant position).

PALM OIL

PO is the most widely used vegetable oil in the world. It is obtained from an ancient tropical palm tree (*Elaeis guineensis*) and it was one of the major sources of dietary fats for centuries in most of West Africa (11). Palm kernel oil (PKO) is extracted from the seeds and edible PO from the mesocarp. PKO has a composition different from that of PO and is mainly used for nonedible purposes (4). Compared with most other vegetable oils, PO contains a high amount of saturated fat (8). Crude palm oil (known also as red palm oil), contains both compounds beneficial to health (such as TAG, vitamin E, carotenoids and phytosterols) as well as impurities (phospholipids, free FA [FFA], gums, and lipid oxidation products). Both can be removed by refining processes, but the composition of the final product is dependent on the refining method (chemical or physical). High-quality PO containing more than 95% neutral TAG, less than 0.5% FFA and a low impurity content is used in the food industry. Low-quality oils are used in nonedible industry (6).

PO represents approximately one-third of the world's vegetable oil production, and its consumption has increased rapidly in the past several decades (8). Malaysia and Indonesia are the main producers of PO, but the *E guineensis* palm tree is now widespread throughout the tropical areas of America and South East Asia. Productivity of PO per unit area is 11, 10, and 7 times the yield of the other main vegetable oils, soybean, sunflower and rapeseed, respectively (4). Environmental and economic aspects of PO production (such as rainforest destruction, biofuels, and child-labour) are widely discussed by journalists, consumers, public, and industry via internet and social media (eg, *https://www.theguardian.com/environment/palm-oil*). These aspects are beyond the scope of this article.

PO has 2 major fractions. Palm olein (POL; 65%–75%) is the low-melting liquid fraction used mainly in cooking oil for frying and in margarines. The high-melting solid fraction, palm stearin (30%–35%), is present in shortenings and hydrogenated oils used as butter substitutes in some countries. PO is generally found in baked goods, cereals, confectionary fats, frozen meals, ice cream, industrial frying fats, margarines, nondairy creamers, salad dressings, supplements/vitamins, and other food products (6).

PO contains 50% SFA, mostly PA (44%) and lower amounts of stearic acid (5%), 40% MUFA, mostly oleic acid, and 10% PUFA, mostly linoleic acid. Thus, PA is the principal constituent of refined PO. FA in PO (as in all vegetable oils) are mainly structured as TAG having oleic acid predominantly located at the SN-2 position, and PA mainly (over 70%–80%) located at the SN-1 and SN-3 positions. As in human milk, PA is also the main SFA naturally occurring in animal milk fats, often found at the SN-2 position (beta-position) of TAG—in cow's milk in approximately 40% and in human milk in 60%–80% (3,5–7).

M.F. conducted a trial using beta-palmitate, which was funded by Industry (Cow & Gate, now Nutricia; in 1995) and has received honoraria for attending 2 Consultancy meetings with Enzymotec (a company involved in the manufacture of beta-palmitate for infant formulas).

The authors report the following conflicts of interest outside the submitted work. J.B. reports personal fees and nonfinancial support from AbbVie, Nutricia, Biocodex, personal fees from MSD, Nestlé, Ferring, Walmark. C.C. received research funding from ORDESA Laboratories and Abbott Nutrition. N.E. reports receipt of grants/research supports from National Institutes for Health Research (UK), Prolacta, Bioscience (US) and Danone Early life Nutrition. He also served as member of Advisory board for Danone Early life Nutrition and received payment/honorarium for lectures from Danone Early life Nutrition, Nestle Nutrition Institute, Baxter, and Fresenius Kabi. K.G. reports personal fees from Nutricia, research grants and personal fees from Nestle and Nutricia, and personal fees from Dr Falk. I.H. reports receipt of payment/honorarium for lectures from BioGaia, Nutricia, Nestle, GM pharma, and receipt of payment/honorarium for consultation from Farmas,Chr Hansen. J.H. reports receipt of grants/research supports from Nutricia Advanced Medical Nutrition Netherlands and Danone Medical care (global). F.I. has participated as a clinical investigator and/or consultant and/or speaker for Arla Food, Biogaia, Nestle, Nestle Nutrition Institute, Wyeth, Danone, and Abbott. A.L. received lecture fees and/or nonfinancial support from Baxter, Fresenius, Nestle, and Mead Johnson Nutrition. N.F.M. acknowledges support of the Slovenian Research Agency (P3–0395: Nutrition and Public Health; L3-8213, L3-7538). C.M. reports receipt of grants/research supports from European Commission Innovation Fund Denmark, Nordea-fonden, Arla Foods, Chr. Hansen, USDEC, Gate Foundation. S.J.M. reports receipt of grants/research supports from DSM Nutritional Products, she served as member of advisory board and received payment/honorarium for consultation from Baxter and received payment/honorarium for lectures from Baxter and Fresenius Kabi. E.V. reports grant/research support from Nutricia Italia Spa, Nestle Health Science—Vitaflo Italy, FoodAR srl Italy, PIAM Pharma, and Integrative Care. R.V. reports no conflict of interest. M.D. has received speaker fees from Baxter, Fresenius, Semper, Abbvie, Nestlé, and research support from Baxter and Prolacta.

DOI: 10.1097/MPG.0000000000002307

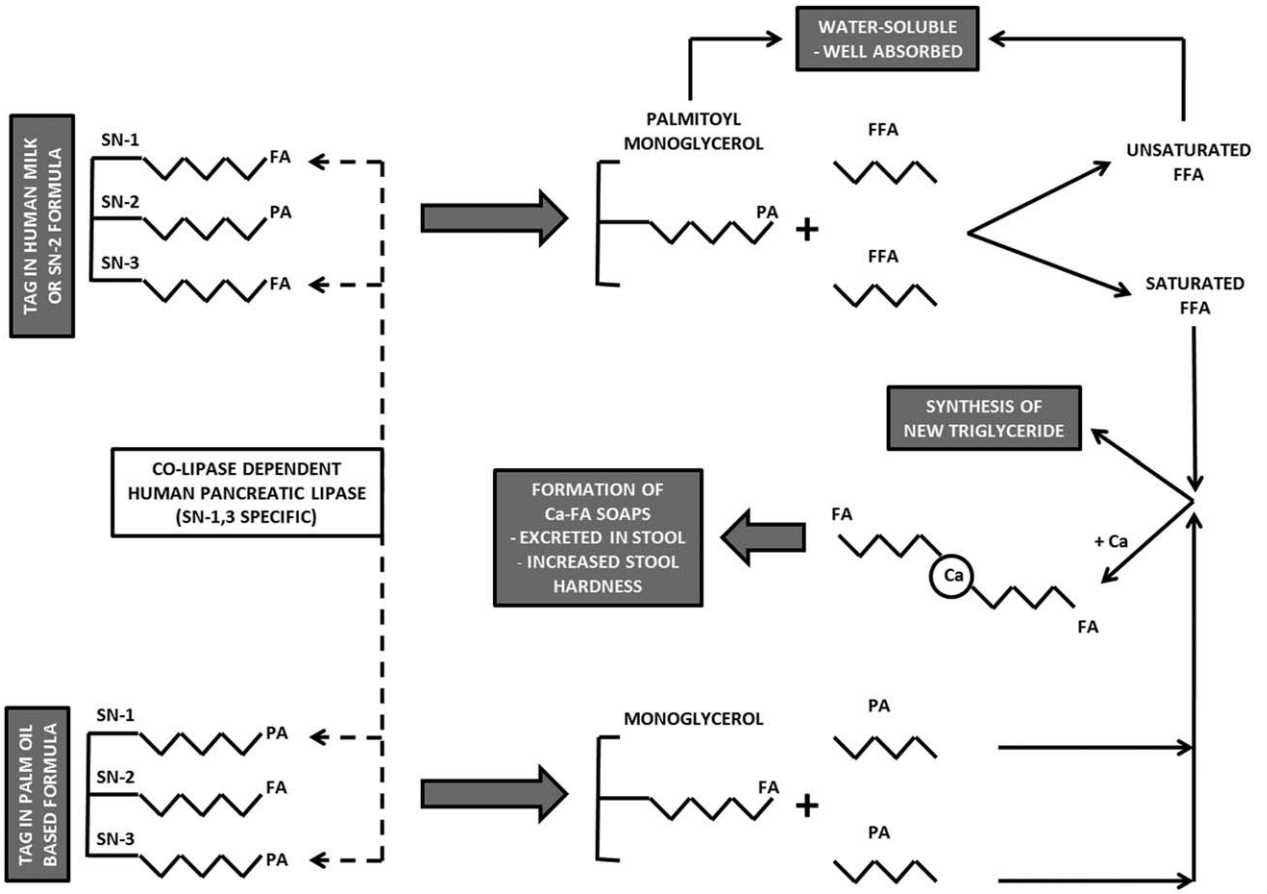

FIGURE 1. Digestion and absorption of triacylglycerol and fatty acids in human intestine. Colipase-dependent pancreatic lipase selectively hydrolyzes the FA at the SN-1 and 3 positions, yielding FFA and the 2-monoglyceride. Unsaturated FFA and monopalmitin are well absorbable. Saturated FFA (including PA) are involved in the re-synthesis of new TAG and/or formation of Ca^{2+} or Mg^{2+} soaps. FA = fatty acids; FFA = free fatty acids; PA = palmitic acid; Ca = calcium.

POTENTIAL HEALTH EFFECTS OF PALM OIL AND PALMITIC ACIDS IN ADULTS

High-fat diets, particularly those rich in SFA, have been linked to cardiovascular diseases (CVD), obesity, type 2 diabetes mellitus (T2DM) and cancer. However, studies on potential unhealthy effects of PO because of the high PA content, are controversial (6,12,13).

Moreover, PO is cholesterol-free and POL, containing a substantial amount of oleic acid (48%), was considered by some authors as a suitable substitute for olive oil in healthy human diets (6). PO has also been suggested as an alternative for partially hydrogenated fats in the food supply to reduce transfat intakes (8). A lower atherogenic power of PO compared with animal fat is also hypothesized, because of the fact that in PO, PA is usually not present at the SN-2 position in TAG and it has been shown in animal experiments that higher percentages of PA at the SN-2 position are related to the most atherogenic profiles (6).

A meta-analysis of 30 articles including 32 clinical trials reported that PO significantly increased both low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol when compared with vegetable oils low in saturated fat, and that PO increased HDL cholesterol when compared with transfat-containing oils (8). The authors of a recent review state that there is not enough evidence to conclude that PO is atherogenic and contributes to elevated serum cholesterol levels (14). A systematic review and meta-analysis of 51 dietary intervention trials (many of them included in the previously mentioned meta-analysis (8) has shown that both favourable and unfavourable changes in blood lipid-related markers of CVD occurred when PO replaced the primary dietary fats (rich in stearic acid, MUFA and PUFA or myristic/lauric acids), whereas only favourable changes occurred when PO replaced trans-FA (15). The same author in a previous review concluded that the evidence on dietary PA or PO and the risk of cancer is not convincing and specific studies are limited (4). There is 1 study showing promising data on potential anti-inflammatory effects of red palm oil and protection against ischemia and reperfusion injuries of the heart in an intensive care setting that merits further investigation (16). Another extensive review reports conflicting results regarding all considered outcomes (T2DM, CVD and cancer) mainly for methodological reasons (6).

There are data from studies on animals and tissue models showing potential negative health effects of PO compared with PO-nonsupplemented diet, such as reduced insulin sensitivity and impaired glucose tolerance, lipotoxicity (negative effect of PA on mitochondrial function mediated by oxidative stress), inflammation in adipose tissue and pancreas, and supposed involvement of PA in regulation of tumour growth (cell proliferation, apoptosis, invasiveness) (6). On the contrary, there are number of animal studies showing potentially beneficial effects of PO on lipid profile (14).

OTHER POTENTIALLY BENEFICIAL OR HARMFUL COMPOUNDS OF PALM OIL

PO is genetic-modification free. Crude PO contains phytosterols, and is the richest natural source of carotenoids (vitamin A precursors), tocopherols, and tocotrienols (vitamin E compounds) (6,11,17). The levels of these compounds are affected to various degrees during processing (personal communication, Specialised Nutrition Europe [SNE]—an association representing food manufacturers, including infant formula producers). The final levels of these compounds in the PO used in the oil blends for infant and follow-on formulas depends on the formula manufacturers' specifications to meet the nutritional profile of these foods. It is important to note that the infant and follow-on formulas fatty acid and vitamin profiles are considered in view of the contribution expected from all ingredients, not just PO. Tocotrienols are natural inhibitors of cholesterol synthesis and recent studies point to their potential beneficial biological properties, such as protection against cancer, cardiovascular diseases, neurodegeneration, oxidative stress, and immune regulation (6,18–20).

On the other hand, PO may contain potentially harmful substances, such as phospholipids, FFA, gums, and lipid oxidation products (6). Glycerol-based process contaminants (glycidyl fatty acid esters [GE], 3-monochloropropanediol [3-MCPD], and 2-monochloropropanediol [2-MCPD], and their fatty acid esters) are found in PO, but also in other vegetable oils, margarines, and some processed foods. The substances form during food processing, in particular, when refining vegetable oils at high temperatures (approximately 200 °C). The European Food Safety Authority (EFSA) points to potential health concerns (genotoxicity, carcinogenicity) of these compounds especially for young age groups. In their recent report, EFSA points out the fact that the intakes of 3-MCPD, especially in exclusively formula-fed infants, slightly exceeded the stipulated tolerable daily intake of $2\,\mu g \cdot kg^{-} \cdot day^{-1}$ (21). Infant formulas that do not contain PO or POL have relatively low concentrations of 3-MCPD and glycidyl esters; however, effective industrial mitigation strategies can substantially lower the content in PO/POL-based formula (22). Infants consuming solely infant formula may be particularly at risk of exposure to GE, however, in recent years, because of voluntary measures taken by producers, levels of GE in PO and fats have fallen substantially (*https://www.efsa.europa.eu/en/press/news/160503a*) (23). Oil blends used in infants and young children nutrition industry contain levels of contaminants (particularly 3-MCPD and GE) in line with regulation as low as is technically possible (SNE, personal communication). Several toolboxes are available and used by the suppliers to mitigate 3-MCPD esters and GE in oils (eg, BLL toolbox—see *https://www.bll.de/de/lebensmittel/sicherheit/unerwuenschte-stoffe-kontaminanten/3-mcpd-und-glycidyl-fettsaeureester/toolbox-minimierung-3-mcpd-glycidyl*). The EU has also recently implemented stricter regulations for foods for infants and young children versus general foods (24).

Some reports show that there may be nonessential trace elements and radionuclides present in PO, originating from water and soil on the palm plantations that may affect the health of consumers. Data are conflicting, the available literature is limited and further research is needed, however, to confirm or refute this suspicion (25).

The aim of this position paper is to review evidence for potential effects of PO and SN-2-palmitate used as source of fat in infant formula on the health of infants and children. Environmental effects of PO production will not be addressed in this article.

MATERIALS AND METHODS

We present the results of relevant studies (RCTs and large observational studies) on possible beneficial or harmful effects of either PO/POL or SN-2-palmitate (beta-palmitate) as a source of fat in infant formulas on the following outcomes: composition of stool; infantile colic; stool frequency and consistency; bone health and growth; metabolic effects (eg, cardiovascular health, T2DM, hypertension, and lipid profile).

The database Medline (via PubMed) and Cochrane Database of Systematic Reviews were searched for keywords for publications up to November 2017—see Appendix 1 (Supplemental Digital Content, *http://links.lww.com/MPG/B600*).

RESULTS

In total, we identified 12 relevant studies using PO/POL (5 on composition of stool, none on infantile colic, 2 on stool frequency and consistency, 3 on bone health and growth, and 2 on metabolic effects) and 21 relevant studies using SN-2-palmitate (8 on composition of stool, 3 on infantile colic, 3 on stool frequency and consistency, 5 on bone health and growth, and 2 on metabolic effects)—see Tables 1 and 2. In the ''Results'' section, studies are reported according to their primary outcome. Secondary outcomes are also mentioned in Tables 1 and 2 and in the ''Discussion'' part of the manuscript. The majority of the identified studies are either industry-supported or performed by employees of formula producers (also mentioned in Tables 1 and 2). The quality of the studies is variable; some have methodological problems, such as very low sample size or the use of multiple interventions (hydrolyzed protein, oligosaccharides, etc).

Palm Oil/Palm Olein Studies

Composition of Stool (Fatty Acid and Calcium Content, Intestinal Microbiota)

We identified 5 RCTs on this topic (26–30), 1 of them composed of 2 subprojects (29) and 2 of them reporting results from the same cohort of patients (26,30) (see Table 1). All were performed on relatively small numbers of healthy term infants. All studies consistently reported lower fat and Ca absorption in infants using PO/POL-based formulas when compared with PO/POL-free formulas. Only 1 study reported equal fat absorption when soy protein-based formula was used, irrespective of its PO content (29). One study also described lower LC-PUFA absorption in POL-based formula (30). None of the studies reported on intestinal microbiota.

Infantile Colic

No relevant study was identified.

Stool Frequency and Consistency

Both a large observational multicentre study and an unblinded RCT (composed of 2 subprojects—first on breastfed and the second on formula-fed infants) have shown less frequent stools and harder stool consistency in term infants fed/weaned to formula containing POL when compared with non-POL formula (31,32).

Bone Health and Growth

Three RCTs were identified—all in healthy term infants with several months of follow-up—focused on bone health and growth (33–35). Two of the studies reported lower bone mineralization (measured by dual-energy X-ray absorptiometry [DEXA]) in the group of infants fed PO/POL-based formula when compared with PO/POL-free formula (34,35). Two of the studies used partially hydrolyzed protein-based formula in both intervention and control arms (33,34). All 3 studies consistently report no difference in

TABLE 1. List of studies evaluating formulas with palm oil/palm olein as source of fat

PO/POL studies												
Clinical outcome	First author, year	Ref. No.	Country	Study design	Sponsor	Type of sponsoring*	Study design	Population	Duration of intervention	Intervention	Comparison	Primary outcome	Secondary outcomes
Composition of stool (FA and calcium [Ca] content, intestinal microbiota)	Leite et al, 2013	(26)	Brazil	Blinded RCT, crossover	Abbott	E, G	Feeding 2 formulas for 14 days in a tolerance period, followed by a 4-day metabolic balance period in 17 of the male subjects	33 healthy term infants (68–159 days of age)	14 days followed by a 4 day hospital ward metabolic balance study	Formula containing POL (44% of total fat), PKO (21.7%), and canola oil (18.5%) as predominant fats (PALM)	Formula not containing POL, PKO or canola oil (NoPALM)	NoPALM group had higher both Ca absorption (%) and retention (%) than PALM group, but absorption was not significant when Ca intake was used as a covariate	NoPALM group had softer stool consistency and higher fat absorption (%) than PALM group. Ca intake was higher in NoPALM versus PALM-fed infants ($P < 0.001$). Formula and human milk intakes, growth, formula acceptability and adverse events were comparable between both groups
	Nelson et al, 1998	(27)	USA	Blinded RCT, crossover	Abbott/Ross	S, G	Comparison of fat and Ca absorption of POL-containing formula versus formula without POL. Fat and Ca levels in the 2 formulas were similar	10 healthy infants (22–192 days of age)	72–96 hours	POL (45% of fat) containing formula	Formula without POL	POL formula-fed infants had lower fat and Ca absorption and higher fat and Ca excretion. The difference in percent fat absorption was explained by significantly ($P < 0.05$) lower % absorption of palmitic (16:0) and stearic (18:0) acids	Stool consistency not determined in this study
	Nelson et al, 1996	(28)	USA	RCT, crossover	Abbott/Ross	S, G	Effect of POL-predominant formula on fat and Ca absorption. Half of infants admitted for 72-hour metabolic studies and half of them performing stool collection at home	11 term infants (27–161 days of age)	72–96 hours	Formula with mixture of 53% POL and 47% soy oil	Formula with mixture of 60% soy oil and 40% coconut oil	Both fat and Ca was less well absorbed in infants using experimental formula, presumably because of the formation of insoluble Ca soaps of unabsorbed PA. The difference in excretion of fat was explained by the difference in excretion of PA	Stool consistency not determined in this study
	Ostrom et al, 2002	(29)	USA	Two blinded RCTs, crossover	Abbott	E, S, G	''Casein hydrolysate study'' and ''soy protein study'' comparing fat and Ca absorption in infants fed either casein hydrolysate-based or soy protein-based infant formulas with or without POL	22 healthy, full-term infants	72 hours	Casein hydrolysate-based (CHF) or soy protein-based (SPF) infant formulas with POL	CHF or SPF infant formulas without POL	Ca and fat absorption was less in infants fed CHF with PO compared with CHF without PO, ($P < 0.01$), but fat and Ca intake did not differ between the 2 groups. For infants fed SPF, fat and Ca intake did not differ between the feeding groups. Mean Ca absorption was also significantly less when infants were fed SPF with PO than when fed SPF without PO ($P < 0.05$). Fat absorption did not differ between the two SPFs. PO, as the predominant fat, is associated with significantly lower absorption of Ca from infant formulas in which Ca salts are the source of Ca.	Secondary outcomes are reported only for the soy-protein study: Infants averaged 1 to 2 stools per day in both groups. Mean rank stool consistency was 3.4 +/- 0.2 for PO and 3.2 +/- 0.2 for no PO group. The percentage of stools that were formed was significantly greater when infants were fed PO formula than no PO formula (57% vs 28%; $P < 0.05$). Percent of feedings with spit-up and vomit did not differ significantly between groups
	Souza et al, 2017	(30)	Brazil	DB-RCT, crossover	Abbott	E, G	Feeding 2 formulas for 14 days in a tolerance period, followed by a 4-day metabolic balance period in 17 of the male subjects	33 healthy term infants (68–159 ± 3 days of age)	14 days followed by a 4-day hospital ward metabolic balance study	Formula containing POL (44% of total fat), PKO (21.7%) and canola oil (18.5%) as predominant fats (PALM)	Formula not containing POL, PKO or canola oil (NoPALM)	NoPALM-fed infants had higher fat absorption (96.55% vs 95.50%, respectively; $P = 0.023$), DHA and ARA absorption, calcium (Ca) retention and nonsignificantly also Ca absorption (58.00% vs 40.9%, $P = 0.104$ when Ca intake was used as a covariate)	The absorption percentage of palmitic acid (C16:0) did not differ significantly, but this acid was excreted at significantly higher concentrations in the PALM (29.42 mg/kg/day) than in the NoPALM (12.28 mg/kg/day). Adverse events did not differ between groups ($p > 0.05$). Stool consistency not determined in this study.

TABLE 1. Continued

PO/POL studies												
Clinical outcome	First author, year	Ref. No.	Country	Study design	Sponsor	Type of sponsoring*	Study design	Population	Duration of intervention	Intervention	Comparison	Primary outcome	Secondary outcomes
Stool frequency and consistency	Alarcon et al, 2002	(31)	USA	Observational multicentre controlled study	Abbott	E, G	Assessment of gastrointestinal tolerance (including stool frequency and consistency) of a new infant milk formula in healthy term infants	6999 healthy term infants (28–98 days of age)	2 weeks	Non-POL formula	Formula containing 45% of POL; other formula; human milk	On the basis of subanalysis of results: less frequent stools and harder stool consistency (both $P < 0.001$) in infants fed formula containing 45% of POL when compared with non-POL formula	There were no statistically significant differences between Non-POL and POL-formula group for the incidence of GI intolerance indicators. Regurgitation not analysed according to POL vs Non-POL.
	Lloyd et al, 1999—part 1	(32)	USA	Unblinded RCT	Abbott/Ross	E	To compare the tolerance of 2 commercially available powder infant formulas that differ in composition. Measures of tolerance in exclusively breastfed infants weaned to an infant formula were evaluated	82 healthy term breastfed infants	2 weeks	Cow milk-based formula with a whey:casein ratio of 60:40 and a fat blend of 45% palm olein, 20% soy, 20% coconut, and 15% high-oleic sunflower oils	Cow milk-based formula with a whey:casein ratio of 48:52 and a fat blend of 42% higholeic safflower, 30% coconut, and 28% soy oils; contained nucleotides	Healthy term breastfed infants weaned to POL-based formula had less frequent stools, fewer brown stools and more yellow stools, and firmer stools than did infants fed control formula without POL	No significant differences in weight gain, spit-up or vomit between feeding groups
	Lloyd et al, 1999—part 2	(32)	USA	Unblinded RCT	Abbott/Ross	E	To compare the tolerance of 2 commercially available powder infant formulas that differ in composition. Measures of tolerance in exclusively formula-fed infants were evaluated	87 healthy term formula-fed infants	2 weeks	Cow milk-based formula with a whey:casein ratio of 60:40 and a fat blend of 45% palm olein, 20% soy, 20% coconut, and 15% high-oleic sunflower oils	Cow milk-based formula with a whey:casein ratio of 48:52 and a fat blend of 42% higholeic safflower, 30% coconut, and 28% soy oils; contained nucleotides	Healthy term formula-fed infants randomised to POL-based formula experienced significantly firmer stools than controls	No significant differences in weight gain, spit-up or vomit between feeding groups
Bone health and growth	Borschel et al, 2014	(33)	USA	Blinded multicentre RCT	Abbott	E, G	Effect of partially hydrolyzed whey-based infant formula with and without POL on growth of healthy term infants	209 healthy term infants	4 months	100% partially hydrolyzed whey formula containing 41% high-oleic safflower oil; 27% coconut oil; 29% soy oil; 1.5% mono- and diglycerides; 0.4% ARA, 0.15% DHA	100% partially hydrolyzed whey formula containing 46% POL; 26% soy oil; 20% coconut oil; 6% high-oleic safflower or high-oleic sunflower oil; 0.64% ARA; 0.32% DHA	There were no significant differences between groups in weight, length, HC, or weight, length or HC gains.	Infants fed PO-free pHF had significantly softer stools than those fed the PO-pHF except at 4 months of age. No statistically significant differences in the number of stools per day between groups during the study. Throughout the study, infants fed PO-free formula had predominantly green stools
	Borschel et al, 2012	(34)	USA	Multicentre DB-RCT	Abbott	E, G	Effect of 2 study formulas on tolerance, BMC and serum vitamin D concentration in healthy term infants	74 term infants (0–8 days of age)	56 or 84 days	Partially hydrolyzed cow's milk whey protein + high-oleic-safflower, soy, and coconut oils (EF)	Partially hydrolyzed cow's milk whey protein + POL, soy, coconut, high-oleic-safflower, and high-oleic-sunflower oil (CF). The CF had less Ca and phosphorus than the EF. The vitamin D3 content was similar in both formulas	Infants fed the EF exhibited significantly greater serum 25-OH vitamin D levels at 2 months of age and significantly greater BMC (assessed by DEXA) at 3 months compared with infants fed CF	Infants fed the EF had softer stools compared with infants fed CF. Incidence of spit-up/vomiting associated with feeding did not differ between groups. No differences were observed in formula tolerance or anthropometric measurements
	Koo et al, 2003	(35)	USA	DB-RCT	Abbott/Ross	E, G	Effect of POL containing formula on bone mineralization in infants	128 healthy term infants (0–2 weeks of age)	6 month	Formula containing PO/coconut/soy/high-oleic sunflower oils (45/20/20/15% oil) (PMF)	Milk-based formula without PO containing high-oleic safflower/coconut/soy oils (40/30/30% oil) (MF)	Bone mineral content (BMC) and bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DEXA) were not different at baseline but infants fed PMF had significantly lower BMC and BMD at 3 and 6 months than infants fed MF	There were no significant differences between both groups in weight, length, head circumference, or formula intake throughout the study

TABLE 1. Continued

PO/POL studies												
Clinical outcome	First author, year	Ref. No.	Country	Study design	Sponsor	Type of sponsoring*	Study design	Population	Duration of intervention	Intervention	Comparison	Primary outcome	Secondary outcomes
Metabolic effects	Fuchs et al, 1994	(36)	USA	RCT	Carnation Nutritional Products	G	Effect of dietary fat on cardiovascular risk factors in infancy.	104 healthy infants (4–6 months of age)	Until 12 months of age	One of 2 nearly identical (except of minor differences in micronutrients) lower fat follow-up formulas (36% kcal from a fat blend of POL, corn, and safflower oils)	Whole cow milk or a standard infant formula (48%–49% of energy as fat from butterfat or a soy-coconut oil blend, respectively)	Mean daily intakes of total fat, saturated fat, monounsaturated fat, and cholesterol as well as mean serum total cholesterol was significantly higher in the infants fed cow milk, whereas mean LDL and apo B were lower in the infants fed the follow-up formulas. Infants consuming the infant formula or whole cow milk demonstrated greater increases in mean serum total cholesterol, LDL, and apo B by 12 months of age compared with infants ingesting follow-up formula	Ponderal, linear, and head circumference growth was equivalent among feeding groups
	Innis et al, 1997	(37)	Canada	Multicentre RCT	Mead Johnson	E, G	Effect of infant formula containing POL on phospholipid and lipid profile, growth and visual acuity in term infants	172 term infants (0–14 days of age)	3 months	Formula containing POL, high oleic sunflower, coconut, and soy oil (22.2% 16:0, 36.2% 18:1, 18% 18:2n-6, 1.9% 18:3n-3)	Formula containing coconut and soy oil (10.3% 16:0 18:6% 18:1, 34.2% 18:2n-6, 4.7% 18:3n-3); breastfed group	Plasma and red-blood-cell phospholipid DHA, AA, cholesterol. and apolipoprotein B (apo B) were significantly lower in the formula- than breastfed infants. There were no differences in visual acuity among the breastfed and formula-fed infants. No significant relations were found between DHA and visual acuity, or AA and growth within or among any of the infant groups. The only difference between the 2 formulas was lower TAG level in non-POL group at day 90 ($P = 0.014$), but there was no difference in TAG levels when compared with breast milk group in any of the formula groups	No significant differences in body weight, length, or head circumference, which could be attributed to breast feeding or formula feeding were found at 1,2, or 3 month of age

apo B = apolipoprotein B; ARA = arachidonic acid; CF = control formula; CHF = casein hydrolysate-based formula; LDL = low-density lipoprotein cholesterol; no PALM = palm oil/palm olein-free formula; PALM = palm oil/palm olein-based formula; PKO = palm kernel oil; PO = palm oil; POL = palm olein SPF = soy protein-based formula, TAG = triacylglycerols.

*Type of sponsoring: E = one of co-authors of the study was employee of the industry; S = study product supplied by industry; G = study supported by grant from/sponsored by industry; U = unclear role of sponsor.

TABLE 2. List of studies evaluating formulas with SN-2-palmitate as source of fat

SN-2-palmitate (beta-palmitate) studies												
Clinical outcome	First author, year	Ref. No.	Country	Study design	Sponsor	Type of sponsoring*	Study aim	Population	Duration of intervention	Intervention	Comparison	Primary outcome	Secondary outcomes
Composition of stool (fatty acids [FA] and calcium [Ca] content, intestinal microbiota)	Bar-Yoseph et al, 2016	(38)	China	Blinded RCT	Enzymotec	E, G	Effect of SN-2 palmitate on FA excretion in term formula-fed infants	171 term infants up to 14 days of age	6 weeks	Infant formula in which 43% of the PA was esterified to the SN2 position (INFAT)	Infant formula containing a standard vegetable oil mixture (13% of the PA at SN-2 position); breastfed group	Significantly lower stool dry weight, fat and PA stool content in the SN2-palmitate formula-fed group compared with the control formula-fed group. Breastfed infants had a significantly lower stool dry weight, fat content, and saponified fat excretion compared with formula-fed infants	No significant differences were observed in any of the anthropometric measurements at baseline or at any visit during the study
	Carnielli et al, 1995: subanalysis of study Carnielli et al, 1995 (40)	(39)	Netherlands	Blinded RCT, crossover	Nutricia	G	Effect of dietary TAG - FA positional distribution on plasma lipid classes and their FA composition in preterm infants	7 preterm infants	1 week	Formula containing 76.1% of PA at the SN-2 position (Betapol)	Formula containing 87.3% of PA at the SN-1,3 positions	Infants fed with SN-2-palmitate formula had higher percentages of PA in plasma sterol esters, TAG, and FFA, and lower linoleic acid in TAG than control formula	Plasma differences were consistent with enhanced absorption of PA from the SN-2 compared with the SN-1,3 positions
	Carnielli et al, 1995	(40)	Netherlands	Blinded RCT, crossover	Nutricia	G	Effect of SN-2 predominant formula on fat and mineral balance	12 preterm (28–32 weeks of gestation) infants at a postnatal age of 38 ± 7 days	2 weeks	Formula with PA esterified mainly at SN-2 position of TAG (Betapol)	Formula with PA esterified mainly at SN-1,3 position of TAG	SN-2-predominant TAG was associated with an improvement in the absorption of myristic, palmitic, and stearic acids and of mineral balance.	Fecal output was not significantly different by treatment. No differences were found in urine production or mean intestinal transit time
	Carnielli et al, 1996	(41)	Netherlands	Blinded RCT	Nutricia	G	Effect of SN-2 predominant formula on fat, fatty acid, and mineral balance	27 healthy term male infants (0–5 weeks of age)	5 weeks	Formula beta (24% palmitic acid, 66% esterified to β-position; Betapol)	Formula intermediate (24% palmitic acid, 39% esterified to the β-position) and regular formula (20% palmitic acid; 13% esterified to the β-position)	Fat absorption was the highest in infants fed the beta formula, intermediate in those fed with the intermediate formula, and lowest in infants receiving the regular formula. Fecal Ca excretion was significantly lower in the beta group than in the other 2 groups	Infants fed the beta formula produced a smaller amount of feces than regular formula group. Consistency and the color of the feces was significantly different among the groups. In the beta group, 2 infants had soft feces, 6 had runnysoft feces, and none had hard stools. All had yellow feces

TABLE 2. Continued

SN-2-palmitate (beta-palmitate) studies												
Clinical outcome	First author, year	Ref. No.	Country	Study design	Sponsor	Type of sponsoring*	Study aim	Population	Duration of intervention	Intervention	Comparison	Primary outcome	Secondary outcomes
	Lambidou et al, 2016	(42)	Germany	RCT	No industry sponsor declared	U	Fecal excretion of FA soaps and total FA in infants fed with regular infant formula, SN-2 palmitate enriched formula and breastfed infants	40 term infants	6 weeks	Infant formula with increased SN-2 palmitate	Breastfed infants; infants fed regular formula	Breastfed infants showed lower fecal excretion of FA soaps and total FA than infants fed with regular infant formula. However, increasing SN-2 palmitate in infant formula did not reduce stool total FA soaps, palmitate soaps and total FA	The results for the safety parameters body weight and head circumference showed no differences among the groups
	Lopez-Lopez et al, 2001	(43)	Spain	Blinded RCT	Fundacio' Bosch i Gimpera, Laboratorios Ordesa, CeRTA	G	The influence of dietary PA-TAG position on the FA, Ca, and Mg contents of at term newborn faeces	36 term infants	2 months	Group B—formula ''a'' (19% PA in SN-2-position) for 2 months and Group C - formula ''a'' during the first month and with formula ''b'' (44.5% PA in SN-2-position) during the second month (Betapol)	Group A— human milk (66% PA in SN-2-position)	Feeding with SN-2-predominant formula reduced significantly the contents of total FA and PA in faeces. Faecal calcium in groups A and C had diminished at 1 month whereas in group B, it remained virtually unchanged	The anthropometric parameters were not significantly different between the 3 groups throughout the study
	Lucas et al, 1997	(44)	UK	Blinded RCT	Wyeth/Unilever	E, S	Effect of infant formula containing synthetic structured TAG on palmitate, total fat, and Ca absorption and Ca soap formation in the gut	24 preterm infants (less than 1500 g and less than 35 weeks of gestation)	3 weeks	Formula containing 74% of SN-2 palmitate (Betapol)	2 comparison diets (8.4% and 28% SN-2 palmitate, respectively)	SN-2 palmitate predominant formula improved palmitate absorption, reduced the formation of insoluble Ca soaps in the stool and improved Ca absorption.	No differences between diet groups were found for steady state gains in weight, length, or head circumference during the whole period on the assigned diets. The infant's sex was found to be unrelated to PA absorption, other individual or total FA absorption, soap excretion or fractional Ca absorption.
	Yaron et al, 2013	(45)	Israel	RCT	Enzymotec	E, G	Effect of high SN-2-palmitate infant formula on the intestinal microbiota of term infants	36 term infants	6 weeks	High SN-2-palmitate formula (HBP group; 44% beta-palmitate from structured PO) (INFAT) not containing pre- or probiotics	Breastfed (BF group) and low SN-2-palmitate (LBP group, 14% beta-palmitate, based on standard unmodified PO; N = 8) formula not containing pre- or probiotics	The HBP and BF groups had higher Lactobacillus and bifidobacteria counts than the LBP group ($P < 0.01$). The Lactobacillus counts at 6 weeks were not significantly different between the HBP and BF groups	At 6 weeks, no significant differences in weight and length were observed between the 2 formula-fed groups; however, the head circumference was lower in the HBP group than in the BF group ($P = 0.019$). z scores for weight, length, and head circumference were found to be within the normal growth range

TABLE 2. Continued

SN-2-palmitate (beta-palmitate) studies												
Clinical outcome	First author, year	Ref. No.	Country	Study design	Sponsor	Type of sponsoring*	Study aim	Population	Duration of intervention	Intervention	Comparison	Primary outcome	Secondary outcomes
Infantile colics	Litmanovitz et al, 2014	(46)	Israel	DB-RCT	Enzymotec	E	Effect of high beta-palmitate formula on crying in term infants	63 healthy term infants	12 weeks	Formula with high SN-2-palmitate (HBP) (INFAT)	Regular formula with a standard vegetable oil mix (LBP); breastfed (BF) infants	The percentage of crying infants in the LBP group was significantly higher than that in the HBP and BF groups both at weeks 6 and 12 (both $P < 0.05$). The infants fed HBP had significantly shorter crying durations when compared with LBP group ($P = 0.047$).	Stool frequency and consistency was comparable in both formula groups. The BF infants had significantly higher stool frequencies and softer stools than the infants in both the formula groups at both 6 and 12 weeks postnatal. At 12 weeks, a significant reduction in hard stools was observed for the HBP group but not the LBP group
	Savino et al, 2003	(47)	Italy	Observational prospective multicentre uncontrolled study	Unknown	U	Effect of high SN-2-palmitate formula on minor feeding problems	604 infants with minor gastrointestinal problems fed up to 90 days of age by study formula	2 weeks	Formula containing fructo- and galacto-oligosaccharides, partially hydrolyzed proteins, low levels of lactose, high SN-2-palmitate and higher density	None	Rreduction in frequency of colic ($P < 0.005$) occurred	Reduction in frequency of regurgitation ($P < 0.005$) and increase in the daily number of stools in constipated children ($P < 0.005$) occurred
	Savino et al, 2006	(48)	Italy	Single-blinded RCT	Numico	G	Effect of partially hydrolyzed formula, with high SN-2-palmitate content and a mixture of galacto and fructo-oligosaccharides on reduction of crying episodes related to infantile colic	267 infants below 4 months of age	2 weeks	Partially hydrolyzed formula, with high SN-2-palmitate content and a mixture of galacto and fructo-oligosaccharides	Standard formula and simethicone	Reduction of crying episodes (both after 1 and 2 weeks) in infants fed experimental formula when compared with standard formula and simethicone ($P < 0.0001$)	None reported
Stool frequency and consistency	Bongers et al, 2007	(49)	Netherlands	DB-RCT, crossover	Nutricia	G	Evaluation of a new infant formula in term infants with constipation	38 constipated term infants (3–20 weeks of age)	3 weeks + cross-over follow-up	Formula containing high concentration of SN-2 palmitate (41%), a mixture of prebiotic oligosaccharides and partially hydrolyzed whey protein	Whey-based control formula (11.5% SN-2 palmitate) partly mixed with a formula based on hydrolyzed whey protein	Feeding with formula containing high concentration of SN-2-palmitate significantly increased defecation frequency (but there was no difference to standard formula [SF]) and had a trend to softer stool consistency when compared with SF. No difference was found in painful defecation or the presence of an abdominal or rectal mass between the 2 groups	Throughout the study, there were no serious adverse effects in either group. Both formulas were well tolerated. Weight gain was similar in both feeding groups

TABLE 2. Continued

SN-2-palmitate (beta-palmitate) studies												
Clinical outcome	First author, year	Ref. No.	Country	Study design	Sponsor	Type of sponsoring*	Study aim	Population	Duration of intervention	Intervention	Comparison	Primary outcome	Secondary outcomes
	Nowacki et al, 2014	(50)	USA	DB-RCT	Nestlé	E, G	Effect of infant formulas containing high SN-2 palmitate with or without oligofructose on stool fatty acid soaps, stool consistency and gastrointestinal tolerance in term infants	165 healthy term infants (25–45 days of age)	4 weeks	Formula containing high SN-2 palmitate plus 3 g/L of prebiotic oligofructose (SN-2+OF)	Control formula (CF); formula containing high SN-2 palmitate (SN-2); human milk-fed group (HM)	Stool consistency score at day 28 of the SN-2 and OF group was lower than CF and SN-2 ($P < 0.0001$), but higher than the HM-fed group ($P < 0.0001$), moreover, SN-2 group was not different from CF. SN-2 group had lower stool palmitate soaps compared with CF ($P = 0.0028$) and SN-2 + OF group had reduced stool palmitate soaps, total soaps and Ca compared with both CF and SN-2 (all $P < 0.0001$). The HM-fed group had lower stool palmitate soaps, total soaps and Ca (all $P < 0.0001$ for each comparison) than all formula-fed groups	The parent assessment of GI tolerance was similar across all groups and the GI burden of each of the study feedings was low. All FF infants had urine osmolality and specific gravity values within the normal range
	Yao et al, 2014	(51)	USA	DB-RCT	Nestlé/Wyeth	E, G	Effects of high SN-2 palmitate infant formulas with and without oligofructose on stool composition, stool characteristics, and bifidogenicity	300 healthy term infants (7–14 days of age)	8 weeks	High SN-2 palmitate formula (40% beta-palmitate) (Betapol); SN-2+3 g/L OF—a high SN-2 palmitate formula supplemented with 3.0 g/L oligofructose (OF); SN-2+5 g/L OF—a high SN-2 palmitate formula supplemented with 5.0 g/L OF	Bovine milk-based term formula with a 100% vegetable fat blend; human milk-fed group (HM)	At week 8 the SN-2 group had 46% less stool soap palmitate ($P < 0.001$) and softer stools than controls. Addition of resulted in even fewer formed stools versus controls. HM group had lowest stool Ca at week 8, OF groups had lower Ca than SN-2 group. both SN-2 ($P < 0.05$) and SN-2 with OF groups ($P < 0.01$) had significantly higher fecal bifidobacteria concentrations than controls at week 8, not differing from HM-fed infants	At weeks 4 and 8, no differences were observed in GI tolerance among any of the feeding groups after adjusting for baseline scores. Mean z scores for weight-for-age, length-for-age, head circumference-for-age, and weight-for-length were similar across all feeding groups

TABLE 2. Continued

SN-2-palmitate (beta-palmitate) studies												
Clinical outcome	First author, year	Ref. No.	Country	Study design	Sponsor	Type of sponsoring*	Study aim	Population	Duration of intervention	Intervention	Comparison	Primary outcome	Secondary outcomes
Bone health and growth	Civardi et al, 2017	(52)	Italy	DB-RCT	Heinz Italia S.p.A.	E, S, G	Effect of infant formula enriched with functional compounds on safety, growth, and support to healthy gut microbiota	51 term neonates	135 days	Formula enriched with galacto-oligosaccharides (7 g/L), SN-2-palmitate (PA was 60% of total FA, whose 39% were esterified at the SN-2 position) and acidified milk (representing 50% of the whole milk in the formula)	Standard formula (SF) based on vegetable oils (including soya oil) and whey protein (enriched in alphalactalbumin)	Infants fed the experimental formula had comparable growth (length, weight, head circumference) to the group receiving standard formula	Infants fed the experimental formula had higher increase of bifidobacteria faecal counts. Gastrointestinal adverse effects, intestinal gas, bowel cramp,s and the mean number of stools per day were comparable between the 2 groups
	Fewtrell et al, 2013—unblinded follow-up of RCT by Kennedy et al, 1999 (54)	(53)	UK	Unblinded follow-up of RCT	MRC UK and EU; original RCT (54) sponsored by Nutricia	G	Long-term effects of formula containing synthetic TAG on bone mineralization evaluated by DEXA	Traceable subjects from original cohort (57 formula-fed and 34 breastfed)	10 years	Formula containing 50% SN-2 palmitate (Betapol)	Standard formula containing 12% SN-2 palmitate. Both formulas contained similar salts, including Ca salts. The control formula had slightly less fat (39 vs 42 g/L); breastfed group	Previously breastfed children had lower lumbar spine BMD SDS (by 0.44, $P = 0.03$), but size-adjusted bone mass did not differ. There were no significant differences in bone mass between the formula-fed groups	The control formula subjects had significantly higher weight SDS than the breastfed subjects, with intermediate values for the high SN-2 group. There were neither significant differences between the groups in the number of children who reported a previous fracture, nor in estimated current daily Ca intake
	Kennedy et al, 1999	(54)	UK	DB-RCT	Nutricia	S	Effects of formula containing synthetic TAG on stool biochemistry, stool characteristics, and bone mineralization	323 healthy term neonates	3 months	Formula containing 50% SN-2 palmitate (Betapol)	Standard formula containing 12% SN-2 palmitate. Both formulas contained similar salts, including Ca salts. The control formula had slightly less fat (39 vs 42 g/L); breastfed group	Infants fed formula containing 50% SN-2 palmitate had higher (but similar as breast-fed infants) whole-body BMC, evaluated by DEXA, softer stools at 6 and 12 wk, and a lower proportion of stool soap FA than infants fed standard formula.	The stools of infants receiving the high–SN-2 formula contained less total FA ($P = 0.013$), however there were no significant differences for the nonsoap FA. A greater proportion of the mothers using the high–SN-2 formula were concerned about runny stools and reported more colic at the age of 3 wk. Duration of crying was not significantly different. Among the formula-fed infants, there were no significant differences in anthropometry throughout the study. There were no significant differences in respiratory tract infections, visits to the family doctor, hospital outpatient visits, or hospital admissions.

TABLE 2. Continued

SN-2-palmitate (beta-palmitate) studies												
Clinical outcome	First author, year	Ref. No.	Country	Study design	Sponsor	Type of sponsoring*	Study aim	Population	Duration of intervention	Intervention	Comparison	Primary outcome	Secondary outcomes
	Litmanovitz et al, 2013	(55)	Israel	DB-RCT	Enzymotec	E	Effect of high beta-palmitate formula on bone strength in term infants	83 term infants	3 months	High SN-2 palmitate formula (43% of PA on SN-2 position; HBP group) (INFAT) based on standard vegetable oil mix of PKO, rapeseed oil, sunflower oil, and PO or structured PO	Regular formula (14% of PA on SN-2 position; LBP group) based on standard vegetable oil mix of PKO, rapeseed oil, sunflower oil, and PO or structured PO; breastfed group	The mean bone SOS (speed of sound measured by quantitative ultrasound) of the HBP group was significantly higher than that of the LBP group ($P = 0.049$) and comparable with that of the breast-fed group	Anthropometric data during study visits showed no significant differences between the 2 formula groups. There was a 2-fold difference in maternal smoking between the 2 formula groups (not statistically significant)—in further analysis not found to affect the change in bone SOS.
	Schmelzle et al, 2003	(56)	Germany	DB-RCT	Numico	E, G	Evaluation of nutritional efficacy and bifidogenicity of a new infant formula containing partially hydrolyzed protein, a high beta-palmitic acid level, and nondigestible oligosaccharides	154 term infants (0–2 weeks of age)	3 months	Infant formula (NF) containing partially hydrolyzed whey protein, modified vegetable oil with a high (41%) SN-2-palmitate content, prebiotic oligosaccharides, and starch	Standard formula (SF) not containing hydrolysed protein or prebiotic oligosaccharides	During the first 6 weeks, NF girls gained more weight and head circumference than the SF girls. These velocity differences were not maintained throughout the 12-week study period	The NF stools had a higher proportion of bifidobacteria at 6 weeks compared with the SF stools, and they were softer. Both formulas were well tolerated
Metabolic effects	Nelson et al, 1999	(57)	Canada	RCT	Ross	S, G	Effect of positional distribution of fatty acids in infant formula triacylglycerols on plasma lipoprotein fatty acids	87 full term infants	4 months	Experimental formula (EF) (fatty acid composition similar to SF, but made with synthesized TAG with 30% SN-2-palmitate) (Betapol®)	Standard formula (SF) (48% of total fat as POL, 26% as soybean oil, 14% as high-oleic acid sunflower oil, and 12% as coconut oil); breastfed group	Infants fed EF, SF, or breast milk had 15.8%, 8.3%, and 28.0% 16:0 in the chylomicron triacylglycerol 2 position ($P < 0.05$). Infants fed EF had significantly lower HDL-cholesterol and apo A-1 and higher apo B concentrations than SF group	There were no significant differences in the weight, length, or HC between the 3 groups during the whole follow-up (120 days)
	Innis et al, 2013	(58)	Canada	RCT	No industry sponsor declared	U	Effect of dietary TAG rich in SN-2 palmitate on post-prandial lipoprotein and unesterified fatty acids in term infants	Healthy infants (120 days of age)	120 days	Formula containing 25%–27% 16:0 with 29% 16:0 at the TAG SN-2 position	Formula containing 25–27% 16:0 with 5% 16:0 at the TAG SN-2 position; Breastfed group	Higher formula SN-2 led to lower n-9-MUFA, but higher n-6-PUFA and n-3-PUFA in the infant plasma, higher 18:0 in LDL TAG, and higher apo B and lower apolipoprotein A-1 (apo A-1).	None reported

apo B = apolipoprotein B; FA = fatty acids; HBP = high beta palmitate formula; LDL = low-density lipoprotein cholesterol; PA = palmitic acid; RCT, randomized controlled trial.
*Type of sponsoring: E = one of co-authors of the study was employee of the industry; S = study product supplied by industry; G = study supported by grant from/sponsored by industry; U = unclear role of sponsor.

anthropometric measurements between PO/POL group and PO/POL-free group.

Metabolic Effects

No relevant intervention studies were found focused primarily on the effect of PO/POL-containing formula on predictors (markers) of metabolic diseases (cardiovascular health, T2DM, hypertension, etc) in infants and children. Two RCTs were identified that focused on lipid profile in healthy infants with several months of follow-up (36,37). A lower serum TAG level at day 90 in the non-POL group when compared with the POL-group was found in the first study but there was no difference in TAG levels when compared with a human milk group in any of the formula groups (37). In the other study, infants consuming POL-based follow-up formula had lower increases in mean serum total cholesterol, LDL, and apo B by 12 months of age compared with infants ingesting the standard infant formula or whole cow milk (36).

SN-2-palmitate (Beta-palmitate) Studies

Composition of Stool (Fatty Acid and Calcium Content, Intestinal Microbiota)

Altogether 8 RCTs were identified on this topic (38–45), 3 of them on preterm infants (39,40,44), the rest on term infants (see Table 2). The study by Carnielli et al (39) was a subanalysis of a study previously published by the same group (40). The studies have consistently shown that a higher SN-2-palmitate proportion in formula is associated with improved absorption of Ca and fat, including palmitate. Only 1 study, presented as a congress abstract only, did not show any reduction in stool total FA soaps, palmitate soaps, and total FA when increasing SN-2 palmitate in infant formula (42). One study has shown higher *Lactobacillus* and *Bifidobacteria* counts in the stool in high SN-2-palmitate group when compared with low SN-2-palmitate group (45).

Infantile Colic

One DB-RCT, 1 single-blinded RCT, and a large uncontrolled observational study were identified, all in term infants (46–48). The DB-RCT tested the effect of SN-2-palmitate alone (46), whereas the other studies used multiple interventions—partially hydrolysed SN-2-palmitate formula containing fructo-oligosaccharides and galacto-oligosaccharides (47,48). All studies have shown a reduction of crying episodes/frequency of colic, when SN-2-palmitate formula was used.

Stool Frequency and Consistency

Three DB-RCTs were identified, all in term infants (49–51). All of the studies used not only SN-2-palmitate, but also prebiotic oligosaccharides as the intervention, moreover, one of them used partially hydrolyzed protein formula (49). The first study showed significantly increased defecation frequency and a trend to softer stools in the intervention arm, but there was no difference compared with standard formula (49). The second study did not show any difference from the control group when only SN-2-palmitate formula was used, however, the stool consistency score was significantly lower at day 28 when both SN-2-palmitate and oligofructose-enriched formula was used (50). In the third study, the SN-2-palmitate group had significantly softer stools than controls at week 8. Addition of oligofructose resulted in even fewer formed stools (51).

Bone Health and Growth

Four RCTs (one of them with unblinded follow-up) in healthy term infants were identified (52–56). Two of the studies were focused on bone health and both have shown short-term positive effects of SN-2-palmitate formula on bone parameters—bone mineral content (BMC) and mean bone speed of sound (SOS) at week 12 (54,55), however, unblinded follow-up of 28% of the original cohort until 10 years of age did not show long-term persistence of this effect (53). The other 2 studies focused on anthropometric parameters and did not show any significant difference at week 12 and/or 135 days of follow-up, respectively, between SN-2-palmitate and control formulas. The experimental formula in both studies was enriched also with prebiotic oligosaccharides, and in one of the studies also contained partially hydrolyzed protein, in the other study acidified milk (52,56).

Metabolic Effects

No relevant intervention studies focused primarily on the effect of SN-2-palmitate formula on predictors (markers) of metabolic diseases (cardiovascular health, T2DM, hypertension, etc) in infants and children were found. Two studies on healthy term infants that focused on lipid profile were identified.

The first RCT showed higher (closer to breastfed group) content of C16:0 FA in the SN-2 position of chylomicron TAG in infants fed SN-2-palmitate formula when compared with standard formula (57). In the other study, higher formula SN-2 led to lower n-9-MUFA, but higher n-6-PUFA and n-3-PUFA in the infant plasma, higher C18:0 in LDL TAG, and higher apo B and lower apolipoprotein A-1 (apo A-1) (58).

DISCUSSION

In cow milk and infant formulas, PA predominantly found in the SN-1 and SN-3 positions is hydrolyzed by pancreatic lipase and the resulting free PA may form Ca-FA complexes, which are poorly absorbed—this was previously confirmed by experiments in rodents and piglets (54,59–65). The overall efficacy of fat absorption gradually increases both in preterm and term infants postnatally reflecting the functional development of the gut (66).

Several studies have shown that PO, as the predominant fat source, or PA present predominantly on SN-1,3 position, may negatively influence absorption of Ca and FA from infant formulas (26–30), and SN-2 palmitate positioning has generally an opposite effect (38,40,41,43–45). One study presented as a congress abstract did not show any effect of SN-2 palmitate on reduction in stool total FA soaps, palmitate soaps, and total FA (42). Despite varying quality of the studies, there is generally convincing evidence of differences in PA digestion and absorption related to positioning of PA on the TAG. No clinical conclusions can be directly made from these findings, but such changes may be relevant to underlying physiological mechanism for some clinical conditions, such as infantile colic or constipation and explain the observed effects on bone health. Moreover, different structure of TAG in infant formulas may influence intestinal microbiota, but the number of studies is limited and no clinically relevant conclusions are possible at the moment (45,51,52,56).

There are 2 RCTs published so far on the effect of high SN2-palmitate formula on crying episodes in infantile colic (46,48). The first study did not only evaluate the effect of SN-2-palmitate as the study formula also contained hydrolyzed protein, a mixture of galacto- and fructo-oligosaccharides, and had different whey/casein ratio and carbohydrate content than control formula. Simethicone was added to standard formula in the control group. Whether the

clinical effect was because of the PO content is, therefore, unclear (48). In the second study, the formulas differed only in SN-2-palmitate content and a reduction in crying was observed. No pre- or probiotics were used (46). Possible beneficial effects on infant colic and other minor gastrointestinal problems were described in a large observational prospective trial; however, the study formula contained fructo- and galacto-oligosaccharides, partially hydrolyzed proteins and low levels of lactose apart from the SN-2-palmitate, and there was no control group (47). These findings are promising, but more data from well-designed RCTs are needed in order to draw conclusions on the effect of SN-2-palmitate in infant colic. In some of the studies not primarily focused on colic, minor GI problems (spit up, vomiting, ''GI intolerance'') were evaluated as secondary outcomes (29,31,32,34). No difference was found between intervention and control group in any of the studies. Moreover, measurement of the primary outcome in trials focused on infant colic is often subject to discussion as it is very difficult to find an objective measurement for ''crying episodes'' and researchers have to rely on subjective evaluation by parents using various questionnaires. According to a recent consensus paper, limited data suggest that infant formula with a partial hydrolysate, galacto-oligosaccharides/fructo-oligosaccharides and added SN-2-palmitate may be of benefit in reducing infantile colic in formula-fed infants in cases where cow's milk protein allergy is not suspected (67).

Previously, it was reported that formula-fed infants have harder stools than breastfed infants. Ca and FA soaps were the dominant factors significantly related to stool solids and hardness score across the breastfed and formula-fed groups (68). Vandenplas and Salvatore (69) in their review on functional gastrointestinal disorders in infants state that harder stools are frequent in infants fed formula containing POL or PO as the main source of fat. A large observational study and a RCT with 2 sub-studies were published on this topic (having stool frequency or consistency as primary outcome) suggesting that POL content in infant formulas may be responsible for this phenomenon (31,32). However, in the observational study, the 2 formulas differed also in other components (ratio of other oils, Ca and nucleotides content) (31). Also in the RCTs, tested and control formulas differed in other aspects (eg, whey:-casein ratio, content of nucleotides) (32).

A recent meta-analysis of RCTs indicated that infants fed POL-free formulas had significantly softer stools (difference in Mean Rank Stool Consistency score −0.355, 95% CI of −0.472 to −0.239, $P < 0.001$) than infants fed POL-predominant formulas. However, stool frequencies were similar between both groups ($P = 0.6$). Studies included in the meta-analysis had many differences in study design, infant age, formula types, and composition. The meta-analysis did not include clinical data from infants fed human milk or SN-2-palmitate (70). Stool frequency and/or consistency was also mentioned as a secondary outcome in other studies (26,29,33,34). Conclusions from these studies generally support the hypothesis that PO/POL content in formula may be associated with harder stools.

Several studies on the effect of SN-2-palmitate on stool consistency or frequency have been published (49–51). The study by Bongers et al (49) did not show significant difference in the effect of SN-2 formula on stool frequency in constipated infants. However, the authors used 3 different interventions at once (partially hydrolyzed protein, SN2-palmitate, and prebiotics) and the study was considered to be underpowered for its outcomes (71). Two studies showed positive effect of SN-2-formula on stool consistency, which seemed to be enhanced by adding prebiotic oligofructose (50,51). Stool consistency or frequency is also reported as one of the outcomes in other studies on Ca/FA balance, bone health and growth, with conflicting results on the effect of SN-2-palmitate (40,41,46,47,52). Moreover, softer stools may not always be perceived positively by mothers. In the study by Kennedy et al (54), a greater proportion of the mothers using the high SN-2 formula were concerned about runny stools at the age of 3, 6, and 12 weeks. The difference was not seen in the small group of infants who had started solids by 12 weeks but continued to receive the study formula. According to a recent consensus paper, a partially hydrolyzed infant formula with prebiotics and SN-2-palmitate may be considered as a dietary intervention for functional constipation in formula-fed infants (67).

For the effect of PO/POL on bone health, the same pathophysiological background as for stool consistency changes was suggested (formation of Ca-FA complexes leading to poor Ca absorption). In an animal model, levels of intestinal calbindin-D9k (vitamin D-dependent Ca-binding protein) mRNA expression was higher in piglets fed PO-based formula when compared with formula with SN-2 predominant synthetic TAG (72). BMC, bone area (BA), and cortical BA in femur were lower ($P = 0.002$, $P = 0.005$, and $P = 0.02$, respectively) in piglets fed human milk fat substitute with a modified TAG structure holding C16:0 predominantly in the SN-2-position compared with a control (63).

In healthy infants, average BMC and bone mineral density (BMD) significantly increases during infancy, and body size is the dominant predictor of bone mineral status (73). Reference values of body composition obtained by DEXA both in preterm and term neonates were published (73–75); however there is a large variation in published normative data for BMC and BMD of both human milk-fed and formula-fed infants (76).

Jones et al (77) have shown in a longitudinal observational cohort study (N = 330) a positive association between breast-feeding in early life (particularly for 3 months or longer) and bone mass in 8-year-old children born at term. Schanler et al have shown that although predominantly formula-fed preterm infants had significantly greater BMC values at 16, 25, and 52 weeks, if the predominantly human-milk fed infants continue to receive human milk, radius BMC will *"catch-up"* to that of similar infants given formula in the posthospitalization period (78). On the contrary, some studies find that human milk-fed infants have lower bone accretion than do formula-fed infants (with greater bone accretion when the mineral content of formula is higher).

Inclusion of PO in infant formula may be responsible for reduced bone mineral accretion, but other factors play a role, like maternal nutritional status (vitamin D, Ca) during pregnancy, type of infant feeding, Ca and phosphorus content of infant formula, infant vitamin D supplementation, diet, and physical activity during the toddler and preschool years (79). A small RCT on 67 infants indicates that during the first 6 months, bone mass accretion is lower in infants fed human milk or low-mineral (Ca and phosphorus) formula compared with infants fed moderate-mineral formula. However, the human milk-fed group had greater bone mass accretion during the second 6 months and by 12 months of age, there were no differences among the feeding groups (80).

A RCT by Koo et al (35) showing that infants fed PO-based formula had significantly lower BMC and BMD at 3 and 6 months than PO-free formula was challenged in 2004 by Clandinin et al (76) because of lack of inclusion of a human milk control group. Infants fed human milk have BMC and BMD values well below either of the 2 study formulas and all are well within published normative values at both 3 and 6 months of age (the same is valid for the PO-based formula group after intervention). This questions the clinical significance of the data, as it is not clear whether bone mineral accretion higher than that found in breastfed infants is beneficial (76). Another RCT has shown higher BMC and greater 25-OH vitamin D serum levels in children fed PO-free formula when compared with PO formula. However, the PO formula contained less Ca than the PO-free formula (34). A retrospective study that

related DEXA performed at 4 years of age (N = 178) with type of infant feeding identified by history has shown no significant differences in BMC or BMD ($P = 0.51$ and 0.89, respectively) among children who had exclusively consumed human milk (n = 57), an infant formula containing no PO (n = 56) or an infant formula containing PO (n = 65) during the first 4 months of life (81). This study was criticized because of its methodology (retrospective nature not controlling for many potential confounders, possible variability in measurement, and underpowered sample size) (82). The authors' reply to this criticism was that their study was designed to detect a difference of 0.52 SD of bone mineral content between feeding groups (82). A systematic review by Koo et al included 9 publications with non-PO and PO comparison groups in infants between 28 and 42 weeks of gestational age and up to 192 days at study onset. The standardized results were consistently significantly ($P < 0.05$) positive in favour of the feeding with non-PO formulas with respect to increased intestinal fractional absorption of fat, PA and Ca and significantly higher BMC. The authors conclude that avoidance of PO or its substitution with synthetic TAG in infant formulas can prevent this detrimental effect (83).

Although a large RCT has shown possible short-term effects of SN-2-rich formula on bone health in infants (54), in an open-label extension of part of the original cohort, no significant effect was shown by DEXA at 10 years of age (53). Thus, it is questionable if the effect of high-SN-2 is long lasting. Another RCT has shown that palmitic structural distribution may influence (with borderline statistical significance) mean bone speed of sound (SOS; a measure of bone density, microarchitecture, cortical thickness, and elasticity) in term infants (55). In contrast, it has been suggested that SOS changes during infancy may be independent of the type of early diet (84).

A meta-analysis by Yu et al (85) (article in Chinese, only abstract evaluated by authors of this position paper) analyzed the effect of infant formula containing PA at the SN-2 position, formula containing PA at the SN-1, 3 positions and formula without PA on nutrient absorption, BMC, and and stool consistency in infants. Absorption of fat and Ca was lower, faecal excretion of Ca was higher, the BMC was reduced, and the incidence of hard stools was increased when the infant formula provided PA at the SN-1 and SN-3 positions as compared with formula with PA at the SN-2 positions or without PA. However, the authors stress that the conclusions should be used with caution because of the limited quality of evidence (85).

Published studies that did not include growth as primary outcome (26,33–38,43–45,51,52,54–57) did not show any significant differences between PO/POL/SN-2-palmitate base formulas and controls. In an animal experiment, a small but significant improvement in most growth parameters was found in the rats fed beta-palmitate-based diet when compared with controls (86).

No human intervention studies focused primarily on the effect of PO/POL/SN-2-containing formula on biomarkers of metabolic diseases (cardiovascular health, T2DM, hypertension, etc) as the primary outcome in infants and children were identified. Scarce data are available on lipid metabolism both from animal and human studies.

One study using a piglet model showed that mRNA levels of hepatic hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, and 7alpha-hydroxylase (C7H) are higher ($P < 0.05$) and plasma total, HDL, and apo B-containing cholesterol are lower ($P < 0.05$) in formula-fed versus milk-fed piglets, irrespective of the formula TAG source (POL vs synthesized SN-2 predominant TAG). There was no difference in LDL receptor mRNA levels (87). This study shows that important components of lipid metabolism are altered by early diet in an animal model, but POL as source of fat in formula does not seem to play a role. In another study, plasma lipid percentages of C18:1 and C18:2n-6 were higher in piglets fed formula with medium chain triglyceride or coconut oil rather than formulas with C16:0 (from PO or synthesized triglyceride containing predominantly sn-2 C16:0), or sow milk, although the formulas contained similar C18:1 and C18:2n-6 (88).

In the study by Innis et al, only TAG levels at day 90 were lower in POL-free formula than in POL formula; however, neither of the groups had different TAG levels when compared with breastfed infants. Moreover, the study was primarily focused on the effect of n-6 and n-3 FA on growth, visual acuity, and lipid profile in infants. Thus, no direct conclusions can be made on metabolic effects of POL by itself (37). The RCT by Fuchs et al has shown that older infants fed lower fat formula have adequate total energy intake and normal growth and that the fat composition of the diets influenced serum lipid and lipoprotein profiles. The design of the study, however, does not allow any POL-specific conclusions, and POL as source of dietary fat may not necessarily be fully responsible for the above-mentioned metabolic changes (36). Results of an RCT by Nelson and Innis (57) suggest that at least 50% of the dietary SN-2-palmitate is conserved through digestion, absorption, and chylomicron TAG synthesis in breastfed and formula-fed infants. In another study by Innis et al (58), postprandial lipoprotein and unesterified FA levels in term infants were different in children fed SN-2-predominant formula compared with low-SN-2 formula.

SUMMARY

Despite available data on potential benefits of SN-2-palmitate and potential nonbeneficial effects of PO/POL used in infant formulas (3,89,90), the current evidence remains inconsistent and does not allow definite conclusions to be drawn. Published studies have variable methodology, differ in subject characteristics, and some of them are underpowered for the key outcomes. Many of the studies combine different interventions, such as partially hydrolyzed protein, prebiotic oligosaccharides, and in some studies experimental and control formula differ in other aspects-like protein source and composition, carbohydrates, or mineral content. Changes in Ca and PA absorption have been reported that may represent the physiological background for some clinical situations, such as infantile colic, constipation, or lower BMC and BMD. PO/POL seem to be associated with harder stools, on the contrary, SN-2-palmitate use may lead to softer stool consistency. Bone effects seem to be short-lasting. For some of the outcomes (infant colic, faecal microbiota, lipid metabolism), the number of studies is very limited and summary evidence inconclusive. There are no studies published on the effect of PO/POL/SN-2 in infant formulas and long-term outcomes/markers of later diseases (CVD, T2DM, obesity, hypertension, cancer, or long-lasting changes in lipid profile). Growth and infant health-related quality of life seems not to be influenced irrespective of PO/POL/SN-2 content of the formula (91). The majority of the studies are supported by (or performed by employees of) infant formula producers. Moreover, in several studies, high SN-2 palmitate formula remains inferior to breast feeding. Thus, because of the lack of high-quality evidence and inconsistency in the findings of the studies presented here, current guidelines do not mandate the inclusion of high SN-2 palmitate in infant formulas (92,93). EFSA successively rejected 2 health claim petitions for beta-palmitate in 2011 and 2014, respectively (3,94,95). There are also other potential health benefits of high dietary SN-2 palmitate suggested in animals, like reduced gut inflammation in a colitis model and altered tissue endocannabinoid concentrations (7,96,97) that warrant further scientific attention.

CONCLUSIONS AND RECOMMENDATIONS

On the basis of the available data, the ESPGHAN Committee on Nutrition:

1. concludes that inclusion of high SN-2-palmitate fat blend in infant formulas may have short-term effects on stool consistency because of reduced formation of calcium soaps, but cannot be considered essential,
2. concludes that there is insufficient evidence to suggest that PO/POL should be avoided as a source of fat in infant formulas for health reasons,
3. recommends that all producers of infant formulas take measures to minimize levels of glycerol-based process contaminants in infant formulas.

The ESPGHAN Committee on Nutrition recommends further research on:

1. possible long-term health effects of PO/POL/SN-2-palmitate-based infant formulas in well-powered RCTs,
2. presence of nonessential trace elements and radionuclides in PO,
3. potential health benefits of high dietary SN-2 palmitate suggested in animals, such as reduced gut inflammation in a colitis model and altered tissue endocannabinoid concentrations,
4. the potential beneficial/harmful effects of other compounds in PO, like tocotrienols.

DISCLAIMER

ESPGHAN is not responsible for the practices of physicians and provides guidelines and position papers as indicators of best practice only. Diagnosis and treatment is at the discretion of physicians.

REFERENCES

1. Delplanque B, Gibson R, Koletzko B, et al. Lipid quality in infant nutrition: current knowledge and future opportunities. *J Pediatr Gastroenterol Nutr* 2015;61:8–17.
2. Koletzko B. Human milk lipids. *Ann Nutr Metab* 2016;69(Suppl 2): 28–40.
3. Zou L, Pande G, Akoh CC. Infant formula fat analogs and human milk fat: new focus on infant developmental needs. *Annu Rev Food Sci Technol* 2016;7:139–65.
4. Fattore E, Fanelli R. Palm oil and palmitic acid: a review on cardiovascular effects and carcinogenicity. *Int J Food Sci Nutr* 2013;64: 648–59.
5. Lopez-Lopez A, Lopez-Sabater MC, Campoy-Folgoso C, et al. Fatty acid and sn-2 fatty acid composition in human milk from Granada (Spain) and in infant formulas. *Eur J Clin Nutr* 2002;56:1242–54.
6. Mancini A, Imperlini E, Nigro E, et al. Biological and nutritional properties of palm oil and palmitic acid: effects on health. *Molecules* 2015;20:17339–61.
7. Miles EA, Calder PC. The influence of the position of palmitate in infant formula triacylglycerols on health outcomes. *Nutr Res* 2017;44:1–8.
8. Sun Y, Neelakantan N, Wu Y, et al. Palm oil consumption increases LDL cholesterol compared with vegetable oils low in saturated fat in a meta-analysis of clinical trials. *J Nutr* 2015;145:1549–58.
9. Lien EL, Yuhas RJ, Boyle FG, et al. Corandomization of fats improves absorption in rats. *J Nutr* 1993;123:1859–67.
10. Mu H, Hoy CE. The digestion of dietary triacylglycerols. *Prog Lipid Res* 2004;43:105–33.
11. Boateng L, Ansong R, Owusu WB, et al. Coconut oil and palm oil's role in nutrition, health and national development: a review. *Ghana Med J* 2016;50:189–96.
12. Berraaouan A, Abid S, Bnouham M. Antidiabetic oils. *Curr Diabetes Rev* 2013;9:499–505.
13. Teng KT, Chang CY, Chang LF, et al. Modulation of obesity-induced inflammation by dietary fats: mechanisms and clinical evidence. *Nutr J* 2014;13:12.
14. Odia OJ, Ofori S, Maduka O. Palm oil and the heart: a review. *World J Cardiol* 2015;7:144–9.
15. Fattore E, Bosetti C, Brighenti F, et al. Palm oil and blood lipid-related markers of cardiovascular disease: a systematic review and meta-analysis of dietary intervention trials. *Am J Clin Nutr* 2014;99:1331–50.
16. Bengmark S. Nutrition of the critically ill - emphasis on liver and pancreas. *Hepatobiliary Surg Nutr* 2012;1:25–52.
17. Souganidis E, Laillou A, Leyvraz M, et al. A comparison of retinyl palmitate and red palm oil beta-carotene as strategies to address Vitamin A deficiency. *Nutrients* 2013;5:3257–71.
18. Ahsan H, Ahad A, Siddiqui WA. A review of characterization of tocotrienols from plant oils and foods. *J Chem Biol* 2015;8:45–59.
19. De Silva L, Chuah LH, Meganathan P, et al. Tocotrienol and cancer metastasis. *Biofactors* 2016;42:149–62.
20. Meganathan P, Fu JY. Biological properties of tocotrienols: evidence in human studies. *Int J Mol Sci* 2016;17:pii: E1682.
21. Update of the risk assessment on 3-monochloropropane diol and its fatty acid esters. *EFSA* 2018;16:5083.
22. Leigh J, MacMahon S. Occurrence of 3-monochloropropanediol esters and glycidyl esters in commercial infant formulas in the United States. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 2017;34:356–70.
23. Scientific opinion on the risks for human health related to the presence of 3- and 2monochloropropanediol (MCPD), and their fatty acid esters, and glycidyl fatty acid esters in food. *EFSA* 2016;14:426.
24. EFSA panel on dietetic products naa Commission Regulation (2018/290) of 26 February 2018 amending Regulation (EC) No 1881/2006 as regards maximum levels of glycidyl fatty acid esters in vegetable oils and fats, infant formula, follow-on formula and foods for special medical purposes intended for infants and young children. *EFSA* 2018;61:64.
25. Olafisoye OB, Oguntibeju OO, Osibote OA. Trace elements and radionuclides in palm oil, soil, water, and leaves from oil palm plantations: a review. *Crit Rev Food Sci Nutr* 2017;57:1295–315.
26. Leite ME, Lasekan J, Baggs G, et al. Calcium and fat metabolic balance, and gastrointestinal tolerance in term infants fed milk-based formulas with and without palm olein and palm kernel oils: a randomized blinded crossover study. *BMC Pediatr* 2013;13:215.
27. Nelson SE, Frantz JA, Ziegler EE. Absorption of fat and calcium by infants fed a milk-based formula containing palm olein. *J Am Coll Nutr* 1998;17:327–32.
28. Nelson SE, Rogers RR, Frantz JA, et al. Palm olein in infant formula: absorption of fat and minerals by normal infants. *Am J Clin Nutr* 1996;64:291–6.
29. Ostrom KM, Borschel MW, Westcott JE, et al. Lower calcium absorption in infants fed casein hydrolysate- and soy protein-based infant formulas containing palm olein versus formulas without palm olein. *J Am Coll Nutr* 2002;21:564–9.
30. Souza CO, Leite MEQ, Lasekan J, et al. Milk protein-based formulas containing different oils affect fatty acids balance in term infants: a randomized blinded crossover clinical trial. *Lipids Health Dis* 2017;16:78.
31. Alarcon PA, Tressler RL, Mulvaney A, et al. Gastrointestinal tolerance of a new infant milk formula in healthy babies: an international study conducted in 17 countries. *Nutrition* 2002;18:484–9.
32. Lloyd B, Halter RJ, Kuchan MJ, et al. Formula tolerance in post-breastfed and exclusively formula-fed infants. *Pediatrics* 1999;103:E7.
33. Borschel MW, Choe YS, Kajzer JA. Growth of healthy term infants fed partially hydrolyzed whey-based infant formula: a randomized, blinded, controlled trial. *Clin Pediatr (Phila)* 2014;53:1375–82.
34. Borschel MW, G-WS, Brabec BA, et al. Tolerance, bone mineral content, and serum vitamin D concentration of term infants fed partially hydrolyzed whey-based infant formula. *Open Nutr J* 2012;6:71–9.
35. Koo WW, Hammami M, Margeson DP, et al. Reduced bone mineralization in infants fed palm olein-containing formula: a randomized, double-blinded, prospective trial. *Pediatrics* 2003;111 (5 Pt 1):1017–23.

36. Fuchs GJ, Farris RP, DeWier M, et al. Effect of dietary fat on cardiovascular risk factors in infancy. *Pediatrics* 1994;93:756–63.
37. Innis SM, Akrabawi SS, Diersen-Schade DA, et al. Visual acuity and blood lipids in term infants fed human milk or formulae. *Lipids* 1997;32:63–72.
38. Bar-Yoseph F, Lifshitz Y, Cohen T, et al. SN2-palmitate reduces fatty acid excretion in chinese formula-fed infants. *J Pediatr Gastroenterol Nutr* 2016;62:341–7.
39. Carnielli VP, Luijendijk IH, van Beek RH, et al. Effect of dietary triacylglycerol fatty acid positional distribution on plasma lipid classes and their fatty acid composition in preterm infants. *Am J Clin Nutr* 1995;62:776–81.
40. Carnielli VP, Luijendijk IH, van Goudoever JB, et al. 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* 1995;61:1037–42.
41. Carnielli VP, Luijendijk IH, Van Goudoever JB, et al. Structural position and amount of palmitic acid in infant formulas: effects on fat, fatty acid, and mineral balance. *J Pediatr Gastroenterol Nutr* 1996;23:553–60.
42. Lambidou MAB, Jochum F, Nomayo A, et al. Effect of high beta-palmitate infant formula supplemented with galacto-oligosaccharides on stool fatty acid soaps. Conference: 49th annual meeting of the european society for paediatric gastroenterology, hepatology and nutrition, ESPGHAN 2016 Athens Greece. *J Pediatr Gastroenterol Nutr* 2016;62:879.
43. Lopez-Lopez A, Castellote-Bargallo AI, Campoy-Folgoso C, et al. The influence of dietary palmitic acid triacylglyceride position on the fatty acid, calcium and magnesium contents of at term newborn faeces. *Early Hum Dev* 2001;65(Suppl):S83–94.
44. Lucas A, Quinlan P, Abrams S, et al. Randomised controlled trial of a synthetic triglyceride milk formula for preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1997;77:F178–84.
45. Yaron S, Shachar D, Abramas L, et al. Effect of high beta-palmitate content in infant formula on the intestinal microbiota of term infants. *J Pediatr Gastroenterol Nutr* 2013;56:376–81.
46. Litmanovitz I, Bar-Yoseph F, Lifshitz Y, et al. Reduced crying in term infants fed high beta-palmitate formula: a double-blind randomized clinical trial. *BMC Pediatr* 2014;14:152.
47. Savino F, Cresi F, Maccario S, et al. ''Minor'' feeding problems during the first months of life: effect of a partially hydrolysed milk formula containing fructo- and galacto-oligosaccharides. *Acta Paediatr Suppl* 2003;91:86–90.
48. Savino F, Palumeri E, Castagno E, et al. Reduction of crying episodes owing to infantile colic: a randomized controlled study on the efficacy of a new infant formula. *Eur J Clin Nutr* 2006;60:1304–10.
49. Bongers ME, de Lorijn F, Reitsma JB, et al. The clinical effect of a new infant formula in term infants with constipation: a double-blind, randomized cross-over trial. *Nutr J* 2007;6:8.
50. Nowacki J, Lee HC, Lien R, et al. Stool fatty acid soaps, stool consistency and gastrointestinal tolerance in term infants fed infant formulas containing high sn-2 palmitate with or without oligofructose: a double-blind, randomized clinical trial. *Nutr J* 2014;13:105.
51. Yao M, Lien EL, Capeding MR, et al. Effects of term infant formulas containing high sn-2 palmitate with and without oligofructose on stool composition, stool characteristics, and bifidogenicity. *J Pediatr Gastroenterol Nutr* 2014;59:440–8.
52. Civardi E, Garofoli F, Longo S, et al. Safety, growth, and support to healthy gut microbiota by an infant formula enriched with functional compounds. *Clin Nutr* 2017;36:238–45.
53. Fewtrell MS, Kennedy K, Murgatroyd PR, et al. Breast-feeding and formula feeding in healthy term infants and bone health at age 10 years. *Br J Nutr* 2013;110:1061–7.
54. Kennedy K, Fewtrell MS, Morley R, et al. 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* 1999;70:920–7.
55. Litmanovitz I, Davidson K, Eliakim A, et al. High beta-palmitate formula and bone strength in term infants: a randomized, double-blind, controlled trial. *Calcif Tissue Int* 2013;92:35–41.
56. Schmelzle H, Wirth S, Skopnik H, et al. 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* 2003;36:343–51.
57. Nelson CM, Innis SM. Plasma lipoprotein fatty acids are altered by the positional distribution of fatty acids in infant formula triacylglycerols and human milk. *Am J Clin Nutr* 1999;70:62–9.
58. Innis SM, Nelson CM. Dietary triacyglycerols rich in sn-2 palmitate alter post-prandial lipoprotein and unesterified fatty acids in term infants. *Prostaglandins Leukot Essent Fatty Acids* 2013;89:145–51.
59. de Fouw NJ, Kivits GA, Quinlan PT, et al. Absorption of isomeric, palmitic acid-containing triacylglycerols resembling human milk fat in the adult rat. *Lipids* 1994;29:765–70.
60. Innis SM, Dyer R, Quinlan P, et al. Palmitic acid is absorbed as sn-2 monopalmitin from milk and formula with rearranged triacylglycerols and results in increased plasma triglyceride sn-2 and cholesteryl ester palmitate in piglets. *J Nutr* 1995;125:73–81.
61. Lien EL, Boyle FG, Yuhas R, et al. The effect of triglyceride positional distribution on fatty acid absorption in rats. *J Pediatr Gastroenterol Nutr* 1997;25:167–74.
62. Tomarelli RM, Meyer BJ, Weaber JR, et al. Effect of positional distribution on the absorption of the fatty acids of human milk and infant formulas. *J Nutr* 1968;95:583–90.
63. Andersen AD, Ludvig SE, Damsgaard CT, et al. The effect of fatty acid positioning in dietary triacylglycerols and intake of long-chain n-3 polyunsaturated fatty acids on bone mineral accretion in growing piglets. *Prostaglandins Leukot Essent Fatty Acids* 2013;89:235–40.
64. Wan J, Hu S, Ni K, et al. Characterisation of fecal soap fatty acids, calcium contents, bacterial community and short-chain fatty acids in sprague dawley rats fed with different sn-2 palmitic triacylglycerols diets. *PLoS One* 2016;11:e0164894.
65. Innis SM, Dyer R, Nelson CM. Evidence that palmitic acid is absorbed as sn-2 monoacylglycerol from human milk by breast-fed infants. *Lipids* 1994;29:541–5.
66. Rings EH, Minich DM, Vonk RJ, et al. Functional development of fat absorption in term and preterm neonates strongly correlates with ability to absorb long-chain Fatty acids from intestinal lumen. *Pediatr Res* 2002;51:57–63.
67. Vandenplas Y, Alturaiki MA, Al-Qabandi W, et al. Middle East consensus statement on the diagnosis and management of functional gastrointestinal disorders in <12 months old infants. *Pediatr Gastroenterol Hepatol Nutr* 2016;19:153–61.
68. Quinlan PT, Lockton S, Irwin J, et al. The relationship between stool hardness and stool composition in breast- and formula-fed infants. *J Pediatr Gastroenterol Nutr* 1995;20:81–90.
69. Vandenplas Y, Salvatore S. Infant formula with partially hydrolyzed proteins in functional gastrointestinal disorders. *Nestle Nutr Inst Workshop Ser* 2016;86:29–37.
70. Lasekan JB, Hustead DS, Masor M, et al. Impact of palm olein in infant formulas on stool consistency and frequency: a meta-analysis of randomized clinical trials. *Food Nutr Res* 2017;61:1330104.
71. Vandenplas Y, Benninga M, Broekaert I, et al. Functional gastrointestinal disorder algorithms focus on early recognition, parental reassurance and nutritional strategies. *Acta Paediatr* 2016;105: 244–52.
72. Devlin A, Innis SM, Wall K, et al. Effect of medium-chain triglycerides on calbindin-D9k expression in the intestine. *Lipids* 1996;31:547–9.
73. Koo WW, Bush AJ, Walters J, et al. Postnatal development of bone mineral status during infancy. *J Am Coll Nutr* 1998;17:65–70.
74. Koo WW, Walters J, Bush AJ, et al. Dual-energy X-ray absorptiometry studies of bone mineral status in newborn infants. *J Bone Miner Res* 1996;11:997–1002.
75. Rigo J, Nyamugabo K, Picaud JC, et al. Reference values of body composition obtained by dual energy X-ray absorptiometry in preterm and term neonates. *J Pediatr Gastroenterol Nutr* 1998;27:184–90.
76. Clandinin MT, Larsen B, Van Aerde J. Comment on: reduced bone mineralization in infants fed palm olein-containing formula: a randomized, double-blinded, prospective trial. *Pediatrics* 2004;114: 899–900.
77. Jones G, Riley M, Dwyer T. Breastfeeding in early life and bone mass in prepubertal children: a longitudinal study. *Osteoporos Int* 2000;11: 146–52.
78. Schanler RJ, Burns PA, Abrams SA, et al. Bone mineralization outcomes in human milk-fed preterm infants. *Pediatr Res* 1992;31:583–6.
79. Specker B. Nutrition influences bone development from infancy through toddler years. *J Nutr* 2004;134:691S–5S.

80. Specker BL, Beck A, Kalkwarf H, et al. Randomized trial of varying mineral intake on total body bone mineral accretion during the first year of life. *Pediatrics* 1997;99:E12.
81. Young RJ, Antonson DL, Ferguson PW, et al. Neonatal and infant feeding: effect on bone density at 4 years. *J Pediatr Gastroenterol Nutr* 2005;41:88–93.
82. Koo W. Re: neonatal and infant feeding: effect on bone density at 4 years. *J Pediatr Gastroenterol Nutr* 2005;41:681.
83. Koo WW, Hockman EM, Dow M. Palm olein in the fat blend of infant formulas: effect on the intestinal absorption of calcium and fat, and bone mineralization. *J Am Coll Nutr* 2006;25:117–22.
84. Zuccotti G, Vigano A, Cafarelli L, et al. Longitudinal changes of bone ultrasound measurements in healthy infants during the first year of life: influence of gender and type of feeding. *Calcif Tissue Int* 2011;89: 312–7.
85. Yu ZB, Han SP, Zhu C, et al. Effects of infant formula containing palm oil on the nutrient absorption and defecation in infants: a meta-analysis. *Zhonghua Er Ke Za Zhi* 2009;47:904–10.
86. Bar-Maisels M, Gabet Y, Shamir R, et al. Beta palmitate improves bone length and quality during catch-up growth in young rats. *Nutrients* 2017;9:pii: E764.
87. Devlin AM, Innis SM, Shukin R, et al. Early diet influences hepatic hydroxymethyl glutaryl coenzyme A reductase and 7alpha-hydroxylase mRNA but not low-density lipoprotein receptor mRNA during development. *Metabolism* 1998;47:20–6.
88. Innis SM, Quinlan P, Diersen-Schade D. Saturated fatty acid chain length and positional distribution in infant formula: effects on growth and plasma lipids and ketones in piglets. *Am J Clin Nutr* 1993;57: 382–90.
89. Bar-Yoseph F, Lifshitz Y, Cohen T. Review of sn-2 palmitate oil implications for infant health. *Prostaglandins Leukot Essent Fatty Acids* 2013;89:139–43.
90. Havlicekova Z, Jesenak M, Banovcin P, et al. Beta-palmitate - a natural component of human milk in supplemental milk formulas. *Nutr J* 2016;15:28.
91. Hays NP, Mao M, Zhang L, et al. Infant feeding and health-related quality of life in healthy Chinese infants: results from a prospective, observational cohort study. *Health Qual Life Outcomes* 2016;14:116.
92. Alimentarius. C Standard for infant formula and formulas for special medical purposes intended for infants. Codex STAN 72-1981. Adopted as a worldwide Standard in 1981.Amendment: 1983, 1985, 1987, 2011, 2015 and 2016. Revision: 2007. 2016.
93. EFSA panel on dietetic products naa Scientific opinion on the essential composition of infant and follow-on formulae. *EFSA J* 2014;12:3760.
94. EFSA panel on dietetic products NAA Scientific Opinion on the substantiation of a health claim related to beta-palmitate and increased calcium absorption pursuant to Article 14 of Regulation (EC) No 1924/ 2006. *EFSA J* 2011;9:2289–305.
95. EFSA panel on dietetic products naa ScientificOpinion on the substantiation of a health claim related to beta-palmitate and contribution to softening of stools pursuant to Article 14 of Regulation (EC) No 1924/ 2006. *EFSA J* 2014;12:3578–92.
96. Lu P, Bar-Yoseph F, Levi L, et al. High beta-palmitate fat controls the intestinal inflammatory response and limits intestinal damage in mucin Muc2 deficient mice. *PLoS One* 2013;8:e65878.
97. Carta G, Murru E, Lisai S, et al. Dietary triacylglycerols with palmitic acid in the sn-2 position modulate levels of N-acylethanolamides in rat tissues. *PLoS One* 2015;10:e0120424.