Carol Rees Parrish, M.S., R.D., Series Editor

Parenteral Nutrition – Lipid Emulsions and Potential Complications


Manpreet S. Mundi


Bradley R. Salonen


Sara L. Bonnes


Ryan T. Hurt

Intravenous lipid emulsions (ILE) have become a crucial component of parenteral nutrition providing a source of essential fatty acids as well as non-protein calories. However, their use, especially in the long-term setting has been associated with significant complications such as intestinal failure associated liver disease and dyslipidemia. This has led to the quest to identify a lipid emulsion that not only decreases the prevalence of these complications, but can also provide beneficial physiologic effects. Multiple plant and fish based sources of ILE have been identified and are in use throughout the world. The present review focuses on the benefits and adverse effects associated with soybean oil (SO) ILE in addition to discussion of subsequent generations of ILE.

INTRODUCTION

Intravenous lipid emulsions (ILE) are a key component of parenteral nutrition (PN), providing a source of essential fatty acids (EFA) as well as non-protein calories. Development of a stable ILE took decades of work by leaders in the field before the introduction of the first stable ILE (Lipomul®; 15% cotton seed, 4% soy phospholipids, 0.3% ploxamer).[1,2] Unfortunately, due to adverse effects felt to be from the emulsifying agent, as well as a non-extractable toxic substance in cottonseed oil, Lipomul® was removed from the market.[3] Subsequently, work by Wretlind and Schuberth led to the introduction of a soybean oil (SO) based ILE as a 10% SO solution.[4] Since that initial introduction, significant modifications have taken place in subsequent generations of ILE, largely in an effort to reduce omega-6 fatty acid (FA) concentrations.

Manpreet S. Mundi, MD[1] Bradley R. Salonen, MD[2] Sara L. Bonnes, MD[2] Ryan T. Hurt, MD, PhD[1,2]
[1]Division of Endocrinology, Diabetes, Metabolism and Nutrition, Mayo Clinic, Rochester, MN [1]Division of General Internal Medicine, Mayo Clinic, Rochester, MN

Soybean Oil Based ILE (Generation 1)

SO ILE are composed of SO triglycerides enveloped by a phospholipid emulsifier allowing the triglyceride core to remain soluble in an aqueous PN mixture, similar to a chylomicron-like particle.[2] The emulsifiers are typically provided in excess amounts to ensure that particles maintain a size of 200-600 nanometers (nm), thus allowing them to pass through the smallest capillaries.[5] Due to this, a typical composition of first generation ILE is 10-30% SO, 1.2% egg yolk phospholipids, and 2.25% glycerin with calorie content ranging from 10-11 kcal/g depending on concentration.[2,6] Therefore ILE provide an excellent source of calories allowing for a reduction in the amount of dextrose used in PN. This

distribution of calories is important because, after the technique of "hyperalimentation" in the US with a solution of glucose, fibrin hydrolysate, vitamins, and minerals was introduced by Drs. Wilmore and Dudrick, reports began linking the high dextrose, fat-free PN to hyperosmolar, hyperglycemic, non-ketotic diabetic coma, hypoglycemia, hepatic enzyme elevations, fatty liver, and essential fatty acid deficiency (EFAD).[6-8] Meguid et al. subsequently performed a pivotal study showing that providing one-third of daily calories as SO ILE (10% Liposyn®) was associated with lower metabolic complications in 23 men, leading to a gradual change in the U.S. to include ILE in PN.[8]

In addition to serving as a calorie source, SO ILE also contain robust amounts of essential fatty acids, linoleic acid (18:2n-6) and α-linolenic acid (18:3n-3), all of which play a key role in structural stability of membranes, as well as in generation of cellular signaling molecules.[9] Humans lack the ability to synthesize these fatty acids and must obtain them from plant sources such as seed oils.[10] Minimal PN requirements of linoleic acid to prevent EFAD have been estimated to be at least 1% of total calories, with optimal levels being 3-4%, whereas α-linolenic acid requirements are even less at 0.2-0.5% of total calories.[9,11] Given that Intralipid® contains 20% SO, with 52% of the fat as linoleic acid, only 2.9-8.7g/day of lipid or 29-87 mL of Intralipid® would be required to meet the essential fatty acid needs of a 60 kg individual receiving 25 kcal/kg/day.[9]

Despite these benefits, the high ratio of n-6 to n-3 polyunsaturated fatty acids (PUFA) in SO ILE can have adverse effects. These 18-carbon fatty acids are used to make 20- and 22-carbon derivatives including arachidonic acid (AA, 20:4n-6) and eicosapentaenoic (EPA, 20:5n-3) and docosahexaenoic (DHA, 22:6n-3).[2,11] AA can be further metabolized to give rise to pro-inflammatory eicosanoids (2-series prostaglandins and thromboxanes, and 4-series leukotrienes).[6,10,12,13] On the other hand, EPA, which originates from n-3 PUFAs, tends to generate less pro-inflammatory 3-series prostaglandins and thromboxanes, as well as the 5-series leukotrienes. In addition to these pro-inflammatory metabolites, SO ILE have also been noted to lead to reduced clearance of the reticuloendothelial system (RES), a key player in the phagocytosis of microorganisms, tissue debris, and particulate matter.[14] With provision of SO ILE at a rate of 0.13 g/kg/hr over 10 hrs daily for 3 days, RES clearance fell by an average of 40%.[14] In a 60kg individual, this would amount to 39 mL/hr of 20% lipid emulsion, which typically has 50g per 250 ml.

SO ILE can also lead to increased LDL and triglyceride levels as well as a decrease in HDL levels. This is due to the liposomes created from excess phospholipid emulsifier acquiring cholesterol and apolipoproteins from HDL in exchange for phospholipids.[15,16] The capacity of HDL to handle this phospholipid influx is saturable, and if infusion rates exceed this capacity, liposomes begin to accumulate in plasma where they can continue to be enriched in cholesterol and begin to show characteristics of lipoprotein-X (Lp-X).[17] It is important to note that 20% ILE tend to have lower phospholipid to triglyceride ratios compared to 10% ILE, resulting in faster phospholipid clearance. Twenty percent ILE are predominantly used in clinical practice.[18]

Another common complication of PN is intestinal failure associated liver disease (IFALD) affecting 30-60% of children and 15-40% of adults requiring long-term SO ILE.[2] IFALD tends to vary in clinical presentation and can include hepatic steatosis, cholestasis, cholelithiasis, and hepatic fibrosis.[19] Although, the etiology of IFALD seems multifactorial, some studies have revealed a correlation between parenteral lipid intake of ≥1 g/kg/day with higher phytosterol levels.[20] Additionally, elevated levels of phytosterols from SO ILE may be another contributing factor as higher phytosterol levels correlate with severity of IFALD.[21] Typically, only a small percentage (5-10%) of dietary phytosterols are absorbed and play a beneficial role by inhibiting enteral absorption of cholesterol. Unfortunately, with parenteral administration, increased levels of phytosterols enter the circulation leading to higher concentrations as they cannot be converted to bile acids.[22]

Soybean Oil and Medium Chain Triglycerides (SO:MCT 50:50) (Generation 2)

The search for improved sources of ILE following widespread use of SO lipids first led to the use of medium chain triglycerides (MCT). Similar to other triglycerides, MCTs have a glycerol backbone with fatty acids attached, typically composed of between 6 (caprioc) and 12 (lauric) carbon atoms compared to the 13-21 carbon chains of long chain triglycerides (LCTs).[23] In addition to being hydrolyzed faster by pancreatic lipases, MCTs are not incorporated into chylomicrons, and are thus rapidly delivered directly to the liver via portal circulation.[23] In contrast to LCTs,

Table 1. Currently Approved ILE in the United States

Product	Lipid Source	n-6:n-3 ratio	Phytosterols mcg/mL	A-tocopherol level (mg/L)	Linoleic (% weight)	a-Linolenic (% weight)
Intralipid® (Baxter)	100% Soybean oil	7:1	343 ± 6	38	44-62	4-11
Clinolipid® (Baxter)	20% soybean oil 80% Olive Oil	NA	NA	NA	13.8-22	0.5-4.2
Smoflipid® (Frasenius Kabi)	30% soybean oil 30% MCT 25% olive oil 15% fish oil	2.5:1	179 ± 10	200	21.4	2.5

NA- not available

Adapted from Mundi MS, Salonen BR, Bonnes S. Home Parenteral Nutrition: Fat Emulsions and Potential Complications. Nutr Clin Pract. 2016;31(5):629-641. doi:10.1177/0884533616663635.

once delivered to the cell, MCTs are able to passively cross the mitochondrial membrane due to their water-soluble properties and proceed directly for oxidation.

Based largely on these theoretical advantages of MCTs demonstrated primarily in animal models, ILE formulations have included combination MCT/LCT for the past 30 years in Europe. A number of small short-term studies have shown MCT ILE to be beneficial compared to SO ILE in terms of liver function tests, phospholipid to triglyceride ratio, and recovery of RES, although some studies reveal minimal benefit.[24-27] Additionally, a larger prospective RCT showed that MCT/LCT use resulted in phospholipid profiles similar to healthy controls at the end of 4 weeks compared to 100% LCT.[28] Due to the limited data on MCT (in any PN formulations - MCT/ LCT or pure MCT), there is a need for longer-term studies to evaluate the safety and efficacy of these ILE formulations.

Olive Oil (OO) Containing ILE (Generation 3)

In the third generation of ILEs, OO was introduced as an alternative lipid source. OO was seen as a potential substitute for SO because it contains higher amounts of monounsaturated fatty acids (MUFA) and less n-6 PUFAs.[29] During the 1990s, ClinOleic®20% became available and was comprised of 80% OO and 20% SO.[30] Since 18.5% of the fat is linoleic acid, 81-240ml per day would be needed to meet daily EFA needs. Concerns were raised that patients may not get these doses and may develop EFAD.[31] Despite data showing a significant reduction in α-linolenic acid and higher Mead acid levels, there was no clinical evidence of EFAD and triene:tetraene ratios remained normal.[31] Studies comparing OO/SO ILE to SO ILE have noted less deterioration of liver enzymes, better phospholipid profile, and improvement in some clinical variables such as ventilator days.[32-34]

Fish-Oil (FO) Containing ILE (Generation 4)

The latest generation of ILE have reduced the SO content by either completely switching to fish oil (FO) alone (Omegaven®; Fresenius Kabi) or using FO in combination with other sources of triglycerides (Smoflipid®; 30% SO, 30% MCT, 25% OO, and 15% FO or Lipoplus; 50% MCT, 40% SO, and 10% FO). FO is an ideal choice for use in ILE given its high content of n-3 PUFA, α-tocopherol, and minimal amounts of plant phytosterols.[35] Omegaven® is currently the only ILE composed entirely of FO, but is not approved for routine use or commercially available in the U.S., and instead is available under study protocols or under a compassionate-use allowance through the FDA for treatment of IFALD.[35] Smoflipid®, on the other hand has recently been approved by the FDA and is now commercially available in the U.S.

Numerous studies have shown significant improvement or reversal of IFALD with the use of FO ILE in the pediatric and adult population.[36,37] Heller et al. studied the impact of combining FO (0.2 g/kg/day Omegaven®) with SO (0.8g/kg/day of 10% Lipovenoes®) versus SO alone (10% Lipovenoes®) in 44 post abdominal surgery patients and noted that the combination of FO with SO resulted in significant decrease in liver enzymes and bilirubin levels.[38] Klek et al. conducted a 4 week-long trial randomizing 73 patients with stable intestinal failure to either Smoflipid® or SO ILE (Intralipid®) and noted that mean ALT, AST,

(continued on page 36)

(continued from page 34)

and total bilirubin concentrations were significantly lower in the Smoflipid® group.[42]

All 3 FO ILE tend to have higher levels of α-tocopherol (~200mg/L) raising plasma concentrations compared to SO ILE.[42,43] A-tocopherol is an antioxidant from the Vitamin E family that is capable of scavenging free radicals that form from peroxidation of lipids, especially PUFAs and can result in cell damage.[44] In addition to raising α-tocopherol concentrations, patients receiving FO ILEs also tend to have lower n-6 PUFA and higher n-3 PUFA concentrations, producing a less pro-inflammatory profile.[43] Metry et al. noted a significantly lower IL-6 level in surgical ICU patients randomized to Smoflipid® compared to Intralipid® on both day 4 and 7 of the trial.[45]

Beyond these liver and anti-inflammatory benefits, studies have also revealed metabolic benefit as patients randomized to Lipoplus® had a greater reduction in free-fatty acids, smaller rise in triglyceride levels, and less reduction in HDL after ~7 days of use compared to the Lipofundin® group.[47] Wu et al. also noted lower triglyceride levels on day 6 in patients randomized to Smoflipid® versus Lipovenoes®.[48]

Of note, most of these trials are very short term and further studies on the long-term impact of FO ILE needs to be evaluated. One area of concern is the development of EFAD given the lower ratio of n-6 PUFAs. Fortunately, clinical trials thus far have revealed that although triene:tetraene ratios do rise, they did not exceed threshold for EFAD if the dose of ILE is ≥1g/kg/day.[49,50] Mead acid levels also remained low again confirming that the rise in Mead acid levels may be largely due to the composition of ILE. An important contributor to the lack of EFAD with fish oil ILE may be their higher content of AA, which is typically derived from linoleic acid.[51]

CONCLUSION

In summary, significant advances have been made since the initial development and administration of ILE. We have progressed from searching for ILE that are non-toxic, to development of ILE that have beneficial properties other than being a source of non-protein, non-carbohydrate calories. Moving forward, additional research is necessary to expand our knowledge regarding the use of later generation of ILE in disease specific situations. The benefits with long-term use also need to be delineated, as much of current research has focused on short-term trials in small cohorts. In order to continue to provide the best care possible to our patients, we need to continue work in this field to not only reduce the risk of harm, but also continue to find ILE that will improve outcomes. ■

References

1. Vinnars E, Hammarqvist F. 25th Arvid Wretlind's Lecture—Silver anniversary, 25 years with ESPEN, the history of nutrition. Clin Nutr. 2004;23(5):955-962.
2. Mundi MS, Salonen BR, Bonnes S. Home Parenteral Nutrition Fat Emulsions and Potential Complications. Nutr Clin Pract. August 2016:884533616663635.
3. Deitel M, Kaminsky V. Total nutrition by peripheral vein — the lipid system. Can Med Assoc J. 1974;111(2):152-154.
4. Schubert O, Wretlind A. Intravenous infusion of fat emulsions, phosphatides and emulsifying agents. Acta Chir Scand Suppl. 13(1961):278.
5. Wanten GJA. Parenteral Lipid Tolerance and Adverse Effects Fat Chance for Trouble? J Parenter Enter Nutr. 2015;39(1 suppl):33S-38S.
6. Vanek VW, Seidner DL, Allen P, et al. A.S.P.E.N. Position Paper Clinical Role for Alternative Intravenous Fat Emulsions. Nutr Clin Pract. 2012;27(2):150-192.
7. Dudrick SJ, Macfadyen BV, Van Buren CT, et al. Parenteral hyperalimentation. Metabolic problems and solutions. Ann Surg. 1972;176(3):259-264.
8. Meguid MM, Schimmel E, Johnson WC, et al. Reduced metabolic complications in total parenteral nutrition: pilot study using fat to replace one-third of glucose calories. JPEN J Parenter Enteral Nutr. 1982;6(4):304-307.
9. Gramlich L, Meddings L, Alberda C, et al. Essential Fatty Acid Deficiency in 2015 The Impact of Novel Intravenous Lipid Emulsions. J Parenter Enter Nutr. 2015;39(1 suppl):61S-66S.
10. Wanten GJ, Calder PC. Immune modulation by parenteral lipid emulsions. Am J Clin Nutr. 2007;85(5):1171-1184.
11. Bistrian BR. Clinical aspects of essential fatty acid metabolism: Jonathan Rhoads Lecture. JPEN J Parenter Enteral Nutr. 2003;27(3):168-175.
12. Tilley SL, Coffman TM, Koller BH. Mixed messages: modulation of inflammation and immune responses by prostaglandins and thromboxanes. J Clin Invest. 2001;108(1):15-23.
13. Lewis RA. Interactions of eicosanoids and cytokines in immune regulation. Adv Prostaglandin Thromboxane Leukot Res. 1990;20:170-178.
14. Seidner DL, Mascioli EA, Istfan NW, et al. Effects of long-chain triglyceride emulsions on reticuloendothelial system function in humans. JPEN J Parenter Enteral Nutr. 1989;13(6):614-619.
15. Meguid MM, Kurzer M, Hayashi RJ, et al. Short-term effects of fat emulsion on serum lipids in postoperative patients. JPEN J Parenter Enteral Nutr. 1989;13(1):77-80.
16. Ferezou J, Bach AC. Structure and metabolic fate of triacylglycerol- and phospholipid-rich particles of commercial parenteral fat emulsions1. Nutrition. 1999;15(1):44-50.
17. Miyahara T, Fujiwara H, Yae Y, et al. Abnormal lipoprotein appearing in plasma of patients who received a ten percent soybean oil emulsion infusion. Surgery. 1979;85(5):566-574.
18. Mirtallo JM, Dasta JF, Kleinschmidt KC, et al. State of the Art Review: Intravenous Fat Emulsions: Current Applications, Safety Profile, and Clinical Implications. Ann Pharmacother. 2010;44(4):688-700.
19. Kelly DA. Intestinal Failure–Associated Liver Disease: What Do We Know Today? Gastroenterology. 2006;130(2, Supplement):S70-S77.
20. Cavicchi M, Beau P, Crenn P, et al. Prevalence of Liver Disease and Contributing Factors in Patients Receiving Home Parenteral Nutrition for Permanent Intestinal Failure. Ann Intern Med. 2000;132(7):525-532.

21. Ellegård L, Sunesson A, Bosaeus I. High serum phytosterol levels in short bowel patients on parenteral nutrition support. Clin Nutr Edinb Scotl. 2005;24(3):415-420.
22. Nandivada P, Cowan E, Carlson SJ, et al. Mechanisms for the effects of fish oil lipid emulsions in the management of parenteral nutrition-associated liver disease. Prostaglandins Leukot Essent Fat Acids PLEFA. 2013;89(4):153-158.
23. Bach AC, Babayan VK. Medium-chain triglycerides: an update. Am J Clin Nutr. 1982;36(5):950-962.
24. Socha P, Koletzko B, Demmelmair H, et al. Short-term effects of parenteral nutrition of cholestatic infants with lipid emulsions based on medium-chain and long-chain triacylglycerols. Nutrition. 2007;23(2):121-126.
25. Nijveldt RJ, Tan AM, Prins HA, et al. Use of a mixture of medium-chain triglycerides and longchain triglycerides versus long-chain triglycerides in critically ill surgical patients: a randomized prospective double-blind study. Clin Nutr Edinb Scotl. 1998;17(1):23-29.
26. Lai H-S, Lin W-H, Wu H-C, et al. Effects of a medium-chain triacylglycerol/long-chain triacylglycerol fat emulsion containing a reduced ratio of phospholipid to triacylglycerol in pediatric surgical patients. Nutrition. 2005;21(7–8):825-830.
27. Kuse ER, Kotzerke J, Müller S, et al. Hepatic reticuloendothelial function during parenteral nutrition including an MCT/LCT or LCT emulsion after liver transplantation - a double-blind study. Transpl Int Off J Eur Soc Organ Transplant. 2002;15(6):272-277.
28. Martin-Pena G, Culebras J, De la Hoz-Perales L, et al. Effects of 2 lipid emulsions (LCT versus MCT/LCT) on the fatty acid composition of plasma phospholipid: a double-blind randomized trial. J Parenter Enter Nutr. 2002;26(1):30-41.
29. Thomas-Gibson S, Jawhari A, Atlan P, et al. Safe and efficacious prolonged use of an olive oil-based lipid emulsion (ClinOleic©) in chronic intestinal failure. Clin Nutr. 2004;23(4):697-703.
30. Vanek VW, Seidner DL, Allen P, et al. A.S.P.E.N. Position Paper: Clinical Role for Alternative Intravenous Fat Emulsions. Nutr Clin Pract. 2012;27(2):150-192.
31. Gramlich L, Meddings L, Alberda C, et al. Essential Fatty Acid Deficiency in 2015: The Impact of Novel Intravenous Lipid Emulsions. J Parenter Enter Nutr. 2015;39(1_suppl):61S-66S.
32. Pálová S, Charvat J, Kvapil M. Comparison of Soybean Oil- and Olive Oil-based Lipid Emulsions on Hepatobiliary Function and Serum Triacylglycerols Level during Realimentation. J Int Med Res. 2008;36(3):587-593.
33. Huschak G, Nieden K zur, Hoell T, et al. Olive oil based nutrition in multiple trauma patients: a pilot study. Intensive Care Med. 2005;31(9):1202-1208.
34. Siqueira J, Smiley D, Newton C, et al. Substitution of Standard Soybean Oil with Olive Oil-Based Lipid Emulsion in Parenteral Nutrition: Comparison of Vascular, Metabolic, and Inflammatory Effects. J Clin Endocrinol Metab. 2011;96(10):3207-3216.
35. Fell GL, Nandivada P, Gura KM, Puder M. Intravenous Lipid Emulsions in Parenteral Nutrition123. Adv Nutr. 2015;6(5):600-610.
36. Premkumar MH, Carter BA, Hawthorne KM, et al. Fish Oil–Based Lipid Emulsions in the Treatment of Parenteral Nutrition-Associated Liver Disease: An Ongoing Positive Experience123. Adv Nutr. 2014;5(1):65-70.
37. Burns DL, Gill BM. Reversal of Parenteral Nutrition–Associated Liver Disease With a Fish Oil–Based Lipid Emulsion (Omegaven) in an Adult Dependent on Home Parenteral Nutrition. J Parenter Enter Nutr. 2013;37(2):274-280.
38. Heller AR, Rössel T, Gottschlich B, et al. Omega-3 fatty acids improve liver and pancreas function in postoperative cancer patients: Omega-3 Fatty Acid After Cancer Surgery. Int J Cancer. 2004;111(4):611-616.
39. Manzanares W, Dhaliwal R, Jurewitsch B, et al. Parenteral Fish Oil Lipid Emulsions in the Critically Ill: a Systematic Review and Meta-analysis. JPEN J Parenter Enteral Nutr. 2014;38(1):20-28.
40. Li N-N, Zhou Y, Qin X-P, et al. Does intravenous fish oil benefit patients post-surgery? A meta-analysis of randomised controlled trials. Clin Nutr. 2014;33(2):226-239.
41. Wang J, Yu J-C, Kang W-M, et al. Superiority of a fish oil–enriched emulsion to medium-chain triacylglycerols/long-chain triacylglycerols in gastrointestinal surgery patients: A randomized clinical trial. Nutrition. 2012;28(6):623-629.
42. Klek S, Chambrier C, Singer P, et al. Four-week parenteral nutrition using a third generation lipid emulsion (SMOFlipid) – A double-blind, randomised, multicentre study in adults. Clin Nutr. 2013;32(2):224-231.
43. Dai Y-J, Sun L-L, Li M-Y, et al. Comparison of Formulas Based on Lipid Emulsions of Olive Oil, Soybean Oil, or Several Oils for Parenteral Nutrition: A Systematic Review and Meta-Analysis. Adv Nutr Bethesda Md. 2016;7(2):279-286.
44. Brigelius-Flohé R. Bioactivity of vitamin E. Nutr Res Rev. 2006;19(2):174-186.
45. Metry AA, Abdelaal W, Ragaei M, et al. SMOFlipid versus Intralipid in Postoperative ICU Patients. Enliven J Anesth Crit Care Med. 2014;1(6):15.
46. KÖLLER M, SENKAL M, KEMEN M, et al. Impact of omega-3 fatty acid enriched TPN on leukotriene synthesis by leukocytes after major surgery. Clin Nutr. 2003;22(1):59-64.
47. Ma C-J, Wu J-M, Tsai H-L, et al. Prospective double-blind randomized study on the efficacy and safety of an n-3 fatty acid enriched intravenous fat emulsion in postsurgical gastric and colorectal cancer patients. Nutr J. 2015;14.
48. Wu M-H, Wang M-Y, Yang C-Y, et al. Randomized Clinical Trial of New Intravenous Lipid (SMOFlipid 20%) Versus Medium-Chain Triglycerides/Long-Chain Triglycerides in Adult Patients Undergoing Gastrointestinal Surgery. J Parenter Enter Nutr. 2014;38(7):800-808.
49. de Meijer VE, Le HD, Meisel JA, et al. Parenteral Fish Oil as Monotherapy Prevents Essential Fatty Acid Deficiency in Parenteral Nutrition Dependent Patients. J Pediatr Gastroenterol Nutr. 2010;50(2):212-218.
50. Gura KM, Parsons SK, Bechard LJ, et al. Use of a fish oil-based lipid emulsion to treat essential fatty acid deficiency in a soy allergic patient receiving parenteral nutrition. Clin Nutr. 2005;24(5):839-847.
51. Strijbosch RAM, Lee S, Arsenault DA, et al. Fish oil prevents essential fatty acid deficiency and enhances growth: clinical and biochemical implications. Metabolism. 2008;57(5):698-707.