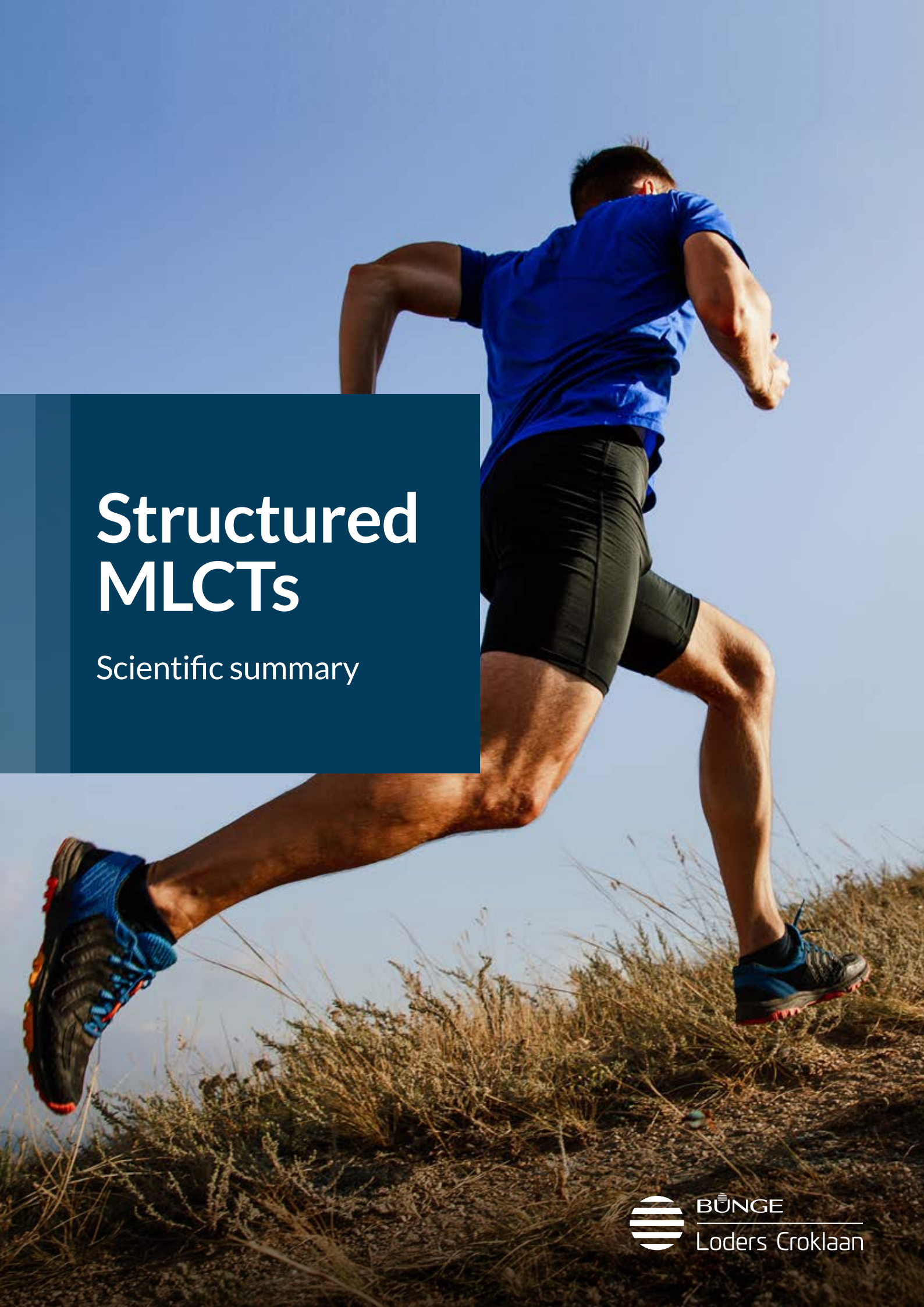
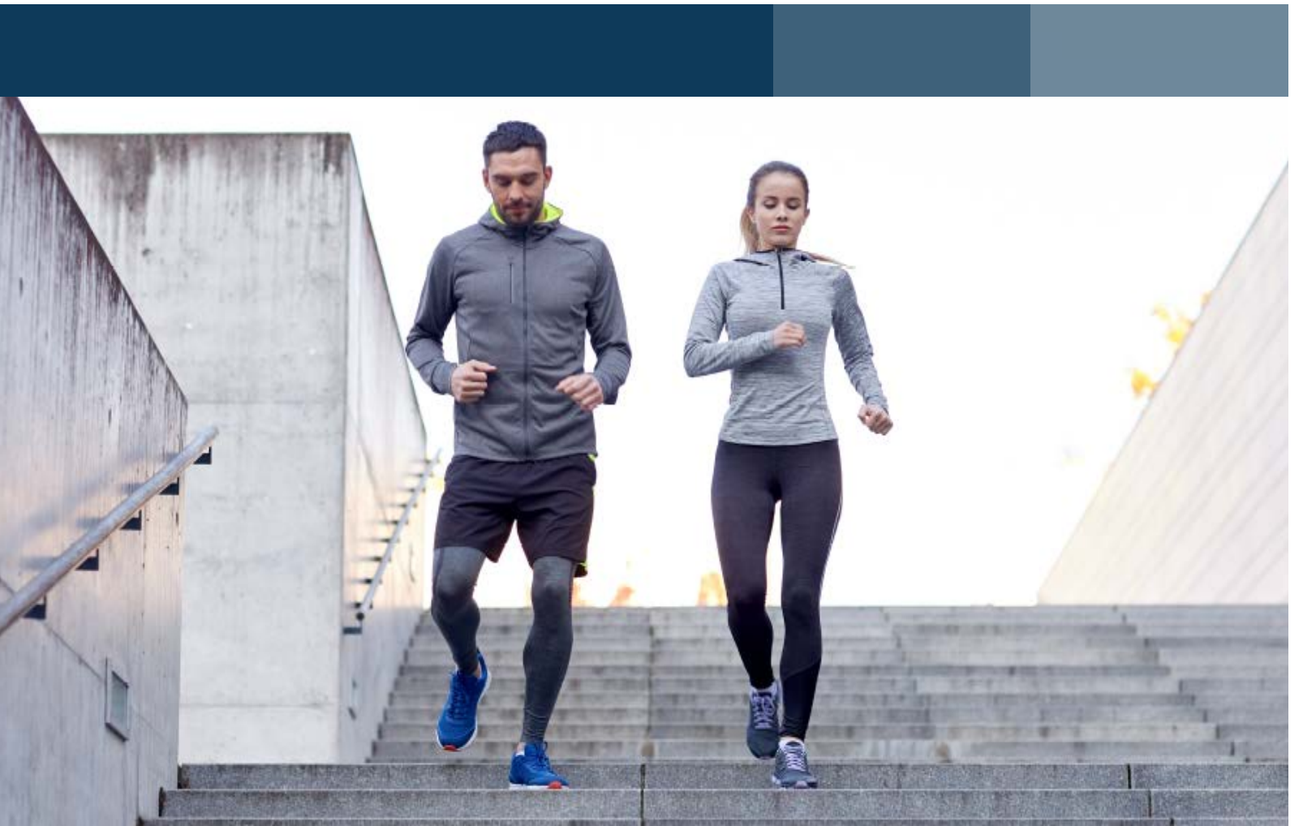


Structured MLCTs

Scientific summary

BUNGE
Loders Croklaan

Table of content

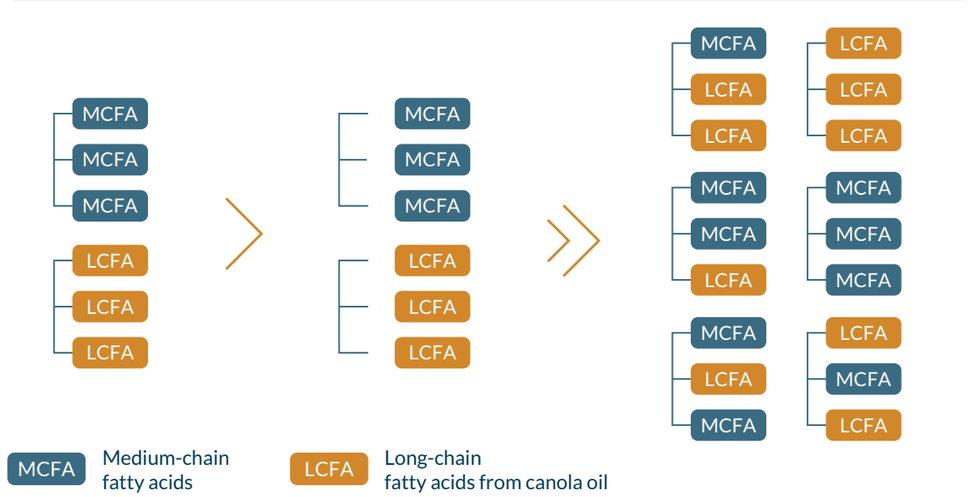


1 Introduction

Structured Medium- and Long-Chain Triglycerides (sMLCTs) are the product of interesterification whereby fatty acids of medium-chain triglycerides (MCTs) and long-chain triglycerides (LCTs) are separated from the glycerol backbone and then randomly recombined to create new structured triglycerides (Figure 1). The newly formed lipid, contains both medium-chain fatty acids (MCFAs), like caprylic (C8:0) and capric (C10:0) acids sourced from coconut or palm kernel oils, and long-chain fatty acids (LCFAs), like oleic (C18:1), linoleic (C18:2) and linolenic (C18:3) acids, typically sourced from canola or soybean oils.

MCTs were first developed to provide a source of energy for individuals diagnosed with various malabsorption, maldigestion, and related disorders. Since then, various preparations for oral, enteral and parenteral use have become available. In order to offset some of the possible complications of using MCTs alone (e.g., essential fatty acid deficiency), preparations consisting of mixtures of MCTs and LCTs were subsequently developed. Structured lipids containing both MCFAs and LCFAs followed. Besides providing the benefits of mixtures of MCTs and LCTs, these sMLCTs showed a series of additional advantages derived from their distinct absorption and distribution within the body.

Figure 1 How traditional MCTs are re-esterified into structured MLCTs



2 Absorption and distribution

Digestion and absorption of fatty acids is affected by the length of their carbon chain (1-3). The longer the chain length, the lower the degree of uptake (1). LCTs are subject to de-esterification in the intestine, resulting in the release of two free LCFAs and the formation of an SN-2 monoacyl-glycerol. These enter the cells that line the intestine, enterocytes, by diffusion. Once inside the enterocyte, LCFAs and monoglycerides are re-esterified into triglycerides and packed with phospholipids, cholesterol ester and apolipopro-teins into structures called chylomicrons. These chylomicrons are released into the lymphatic system from where they drain into the subclavian vein via the thoracic duct. In this manner, LCTs reach the circulatory system to become available to peripheral tissues and become long-lasting sources of energy.

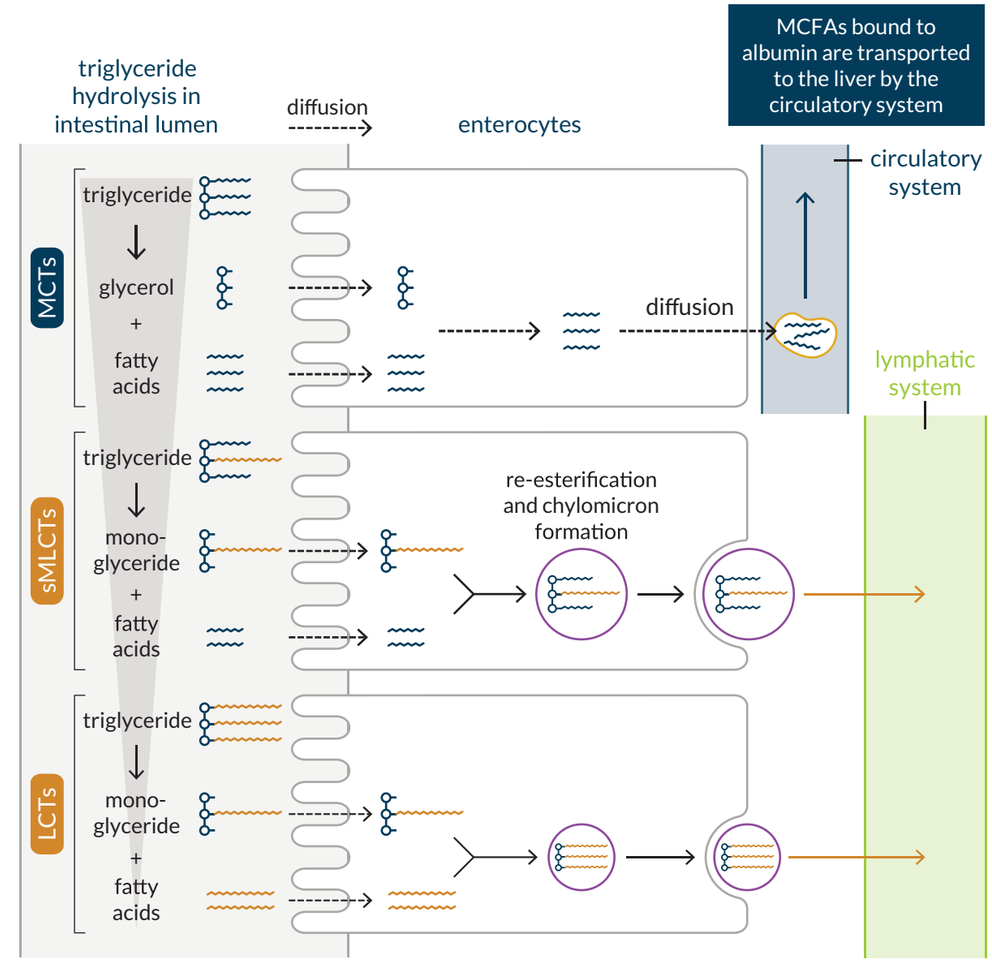
MCTs are processed in a completely different manner. In the intestine, they are hydrolyzed into free MCFAs and glycerol. MCFAs also diffuse into the enterocytes but are, by and large, not re-esterified. Instead, they continue moving by diffusion into the portal vein where they form complexes with albumin (3-7). MCFAs bound to albumin are then directly taken up by the liver (8, 9). In the liver, MCFAs are rapidly catabolized in the mitochondria through ß-oxidation to become a fast source of energy.

Structured MLCTs combine properties of both MCTs and LCTs (10-15). They are de-esterified in the lumen of the intestine and diffuse or get transported into enterocytes as monoglycerides and fatty acids. Inside the enterocyte, the MCFAs, LCFAs, and monoglycerides are mostly re-esterified and follow the chylomicron route to the lymphatic system. These chylomicrons enter the circulation taking MCFAs to peripheral tissues where they can become fast sources of energy (Figure 2) while the LCFAs can be stored for use during tissue repair (Table 1).

Table 1 Comparison of metabolic performance for structured MLCTs, MCTs, LCTs and MCTs/LCTs

	sMLCTs	MCTs	LCTs	Mix of MCTs/LCTs
Absorption route	Hydrolysis into MCFAs, LCFAs and 2-monoacylglycerols. Reformed as triglycerides and packed into chylomicrons within enterocytes. Transport into the thoracic duct to reach systemic circulation (33)	Hydrolysis into MCFAs. Diffussion to the portal vein to reach the liver.	Hydrolysis into MCFAs, LCFAs and 2-monoacylglycerols. Reformed as triglycerides and packed into chylomicrons within enterocytes. Transport into the thoracic duct to reach systemic circulation.	As MCTs and LCTs separately
Absorption speed	Relatively fast, reaching peripheral tissues	Fast, reaching the liver	Slow, reaching peripheral tissues	As MCTs and LCTs separately
Energy supply	Rapid energy sources supply directly to tissues	Rapid energy source supply to the liver	Slow energy source supply to tissues	As MCTs and LCTs separately
Protein Economy	Improve nitrogen balance and increase pre-albumin/albumin levels (34, 35)	Reduced vs. sMLCTs (34, 35)	Reduced vs. sMLCTs (34, 35)	Reduced vs. sMLCTs (34, 35)
Essential Fatty Acids PUFAs	Essential Fatty Acids source	Not a source	Essential Fatty Acids source	As MCTs and LCTs separately
Clearance	Fast clearance (28, 38-41)	Fast clearance	Slow clearance of LCTs from the bloodstream	Slow clearance of LCTs from the bloodstream
Potential Adverse Events (AEs)	Reduced AEs compared to mix of MCTs/LCTs (34, 35)	Potential for metabolic acidosis, ketosis, liver burden.	Reduced AEs compared to MCTs alone.	As MCTs and LCTs separately

Figure 2 Structured MLCTs mechanism of absorption



3 Benefits of structured MLCTs as a functional ingredient

3.1 Medical foods for dietary management of digestive disorders

Medical foods or Foods for Special Medical Purpose (FSMP) are intended for partial or exclusive feeding of individuals under medical supervision. These patients have distinctive nutritional requirements, the management of which cannot be achieved by modification of the normal diet alone. Structured MLCTs are recommended for use in medical food or FSMP in order to manage digestive disorders, in particular, those affecting nutrient absorption.

MCTs, containing shorter chain fatty acids, are digested more easily than LCTs, mainly because MCFAs are absorbed faster (3, 16). Hence, MCTs have been extensively used as source of nutrition in the management of disorders that affect nutrient absorption across all age groups (2, 9, 16-27).

In these applications, ingestion of MCTs is well-tolerated, with side-effects limited to nausea, emesis, borborygmi, diarrhea, abdominal distension and pain. However, long-term usage of MCTs at high doses might have an excessive burden to liver function.
As structured MLCTs combine the characteristics of both MCTs and LCTs, they provide energy sources that are easy to absorb while, at the same time, supporting energy delivery to peripheral tissues, including muscle. This property makes sMLCTs ideal for Oral Nutritional Supplementation (ONS) and enteral (tube) feeding when the recovery of muscle mass and physical condition are part of the treatment's priorities.

Indeed, they have been used in oral supplementation, early enteral feeding, and transition away from total parenteral nutrition in children of one to 13 years of age with conditions like inflammatory bowel disease, cystic fibrosis, celiac disease, pancreatic disorders, short bowel syndrome, malabsorption, and maldigestion. Structured MLCTs have also been used in adults with gastroenteric dysfunction or feeding issues, including short bowel syndrome, bowel resection, malabsorption, pancreatic insufficiency, chronic diarrhea, Crohn's disease, bile salt deficiency, diverticulosis, celiac disease and cystic fibrosis.

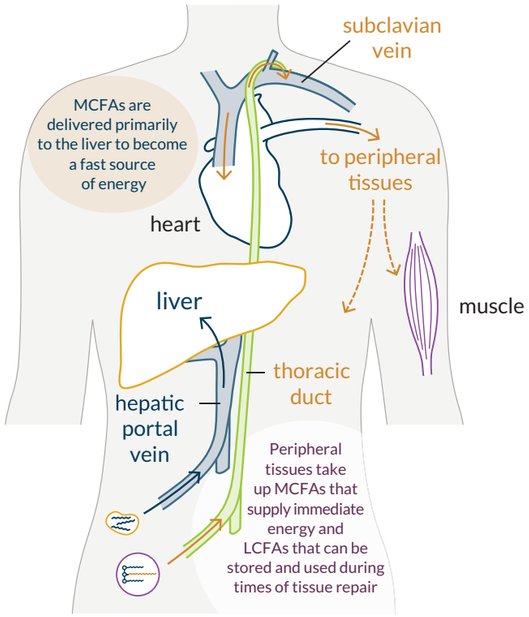
Table 2 Human Studies Conducted with Structured MLCTs under gastrointestinal conditions

Study objective	Assess safety, tolerance and efficacy of ONS containing sMLCT	Assess safety, tolerance and efficacy of a peptide-based enteral diet with sMLCT	Determine the role of malabsorption in plasma and tissue linoleic acid reduction in cystic fibrosis patients
Population	Chronic malabsorption or maldigestion patients (n=35)	Critically ill ICU patients (n=49)	Cystic fibrosis (n=9) and healthy subjects (n=7)
Control	None	High protein enteral formula containing mix of MCTs-LCTs (Osmolite®; n=24)	Safflower oil (with 74% FA as C18:12 microlipid (50% emulsion)
Intervention	Peptide-based oral nutritional supplement (ONS) containing structured MLCT (Vital® 1.5; n=35)	Peptide-based, high protein, high omega-3 diet containing structured MLCT (Vital AF®; n=25)	Structured MLCT (Captex 810D) and MCT (Captex 810B)
Duration	16 days	21 days or until ICU discharge	8h (plasma 0,2 4, 6, 8h after meal)
Design and dosage	Twice daily 220ml	Sole source nutrition; daily max. 1500 ml	36g of lipids in milk shake containing 15g of protein and 45g of carbohydrate on separate days
Summary of results	Significant increase in mean body weight gain, mean body mass index and serum pre-albumin with the sMLCT ONS. No significant changes in total energy, protein, carbohydrate and fat intake and no safety concerns.	Significantly fewer days with adverse events (P=0.03) and undesired gastrointestinal events (p=0.04).	sMLCT treatment (Captex 810D) showed a significant increase in plasma linoleic acid (P<0.01). No difference between control and MCT (Captex 810B).
Reference	Nelson 2019	Seres and Ippolito 2016	McKenna 1985

Table 2 continued

Study objective	Assess safety, tolerance and efficacy of an enteral diet with sMLCT	Investigate, ex vivo, the mechanism for the effects seen in Kenler 1996 by assessing eicosanoid production from peripheral blood mononuclear cells
Population	Upper gastrointenstinal malignancy surgery patients (n=50)	Upper gastrointestinal malignancy surgery patients (n=20)
Control	Isonitrogenous, isocaloric formula containing mix of MCTs-LCTs (n=18)	Isonitrogenous, isocaloric formula containing mix of MCTs-LCTs (n=10)
Intervention	Enteral diet containing structured MLCT-fish oil (n=17)	Enteral diet containing structured MLCT-fish oil (n=8)
Duration	7 days	7 days
Design and dosage	Enteral feeding initiated post-surgery at 10ml/hr; rate increased by 10ml/hr every 12 hours, assessing the ability to reach >40ml/hr	Same as Kenler 1996
Summary of results	sMLCT-fish oil diet showed significant incorporation of EPA into plasma and erythrocyte phospholipids, a 50% decline in the total number of gastrointestinal complications and infections, and improved renal and liver function	Significant reduction in pro-inflammatory eicosanoid (prostaglandin E2 p<0.03 and 6-keto PGF1 alpha p<0.01) production in PBMCs from patients receiving structured MLCT-fish oil.
Reference	Kenler 1996	Swails 1997

Figure 3 Structured MLCTs tissue distribution



3.1.1 Oral nutritional supplementation (ONS)

When individuals are unable to meet their nutritional requirements through diet, ONS is the first line of treatment to allow proper nutrient absorption and prevent or fight malnutrition. Structured MLCTs supplementation has been shown to support faster essential fatty acid absorption than LCTs while meeting the caloric intake needs of patients.
For example, individuals with cystic fibrosis and pancreatic enzyme deficiency with reduced linoleic acid absorption showed significantly increased plasma levels when the essential fatty acid was delivered in a sMLCT compared to a control in which LCTs were used (28).
In a recent prospective, single-arm, single treatment study, a peptide-based ONS containing sMLCTs showed significant increases in mean body weight gain, mean body mass index, and serum prealbumin compared with baseline values (29). These data show that sMLCTs in ONS applications can support individuals with certain medical conditions to meet their nutritional needs.

3.1.2 Enteral feeding

When ONS is not an option to meet a patient's nutritional needs, enteral (tube) feeding is often used. Structured MLCTs also show benefits in this application with lower adverse events than mixes of MCTs and LCTs. Structured MLCTs with MCTs and fish oil have been shown to produce similar clinical chemistry, hematological parameters, and result in similar caloric formula intake compared to a conventional mix of MCTs and LCTs. However, the sMLCT formulas showed better tolerability, safety profile, and reduced eicosanoid production, a proxy for inflammatory signaling (30-32). In one study with 49 critically ill adults in intensive care, requiring enteral tube feeding as their sole source of nourishment (30), the sMLCT group showed fewer days with adverse events, undesirable gastrointestinal disturbances, and distention.
In another study, administration of sMLCT or conventional mix of MCT/LCT formula to 50 cancer patients who had undergone major abdominal surgery for upper gastrointestinal malignancies resulted in improved liver and renal function in the sMLCT group. The total number of days with, and the incidence of gastrointestinal complications were reduced as well (31, 32) . The ability of sMLCTs to meet the primary clinical objectives of treatment with lower adverse events leads, in general, to faster recovery once patients are able to feed by mouth again.

3.2 Sports nutrition and muscle-building

Structured MLCTs are different than traditional MCTs. They deliver rapid sources of energy to peripheral tissues, including muscles, while traditional MCTs are mainly metabolized in the liver. Hence, if MLCTs are available in situations of stress when extra protein building is required, muscles have access to MCFAs to use as source of rapid energy, sparing amino acids for building protein. This has been shown both in animal and clinical studies (10, 33-35).

Animal models have shown that sMLCTs become available to tissues through their lymphatic absorption. In a rat model of fat malabsorption, lymph triglycerides, cholesterol, capric and eicosapentaenoic acids increased rapidly, and were maintained at significantly higher levels when the animals were fed sMLCTs compared to control feed consisting of a mix of MCTs and LCTs (10, 33). When studied in humans, sMLCTs showed improved cumulative nitrogen balance compared to a mix of MCTs and LCTs when fed for 5-7 days with diets containing similar protein load (34, 35, Figure 3). Higher values of pre-albumin and albumin with lower plasma levels of triglycerides and cholesterol were also observed with the structured MLCTs. Improved nitrogen balance and increased pre-albumin levels indicate the MLCTs lead to improved protein economy and better nutritional efficacy. Significantly lower plasma triglycerides and cholesterol suggest faster metabolization of MLCTs compared to mixtures of MCTs and LCTs. Finally, structured MLCTs were also associated with reduced inflammation, as reflected by significantly lower C-reactive protein concentrations which might suggest a more effective role in providing energy during tissue repair and recovery (35).

In sports nutrition and for muscle-building applications, an ingredient leading to more and faster delivery of energy to peripheral tissues results in improved protein economy. Muscles have a readily available source of energy that allows them to perform better and to avoid relying on protein catabolism for recovery and repair.

3.3 Active aging and muscle maintenance

Muscle condition plays an important role in maintaining health and quality of life during aging. Muscle loss occurs when the body breaks down protein faster than it can synthesize it. While muscle mass reaches its peaks at around age of 30, it starts to decline more rapidly after age 40 and continues until 35-40% of total muscle mass and 20-40% of strength is lost, by age 80. If not addressed, muscle loss can threaten health and independence as it becomes debilitating and results in impaired mobility, balance, and increased risk of falls and fractures (36). Age-related conditions, such as loss of bone and muscle mass and strength occur in over 70% of males and 40% of females aged 65 or older (37). Properly addressing muscle health condition during the aging process is therefore critical. Structured MLCTs, due to its absorption and metabolic properties, are an ideal supplement to healthy diets aimed at supporting muscle and strength maintenance in the elderly.

As discussed in previous sections (see 2, 3.2 and Figure 3) structured MLCTs support reduced muscle catabolism and improved nitrogen balance (34, 35) with better absorption and tolerance (28-10, 32) and significantly lower plasma triglycerides and total cholesterol levels (34, 35).

Aging is a natural process whereby the slow loss of muscle mass might have a significant impact on quality of life.
A balanced diet with sMLCT supplementation can provide fast energy supply to muscles, improving protein economy. This, and the additional benefits of reduced plasma triglycerides and total cholesterol levels, provide further support to a longer, active life.

Figure 4 Structured MLCTs

Structured MLCTs and traditional MCTs are not the same

Structured MLCTs

Contain medium- (–) and long-chain (—) fatty acids in the same triglyceride

Traditional MCTs

Contain just medium-chain (–) fatty acids in the triglyceride

Medium chain fatty acids

C8 medium chain fatty acid

C8

C10 medium chain fatty acid

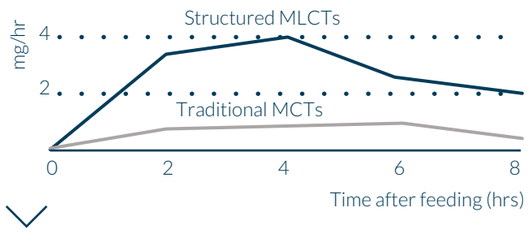
C10

These are the medium chain fatty acids present in Bunge's structured MLCTs

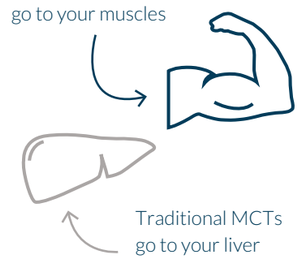
Structure MLCTs deliver sources of rapid energy to your muscles

Structured MLCTs deliver medium chain fatty acids to muscles

Structured MLCTs (—) travel through the circulatory system to your tissues, while traditional MCTs (—) do not. (33)



Structured MLCTs to the muscle

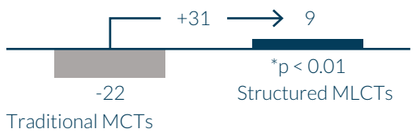


Structured MLCTs promote protein-building in your muscles

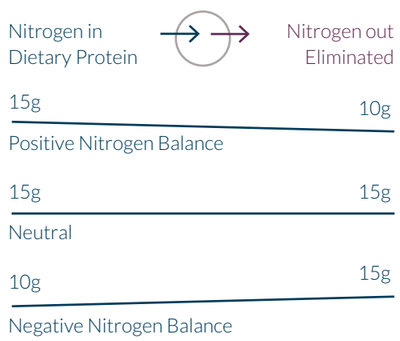
Structured MLCTs improve nitrogen balance in humans

Cumulative nitrogen balance improved significantly in people eating structured MLCTs vs. traditional MCTs with the same dietary protein intake for 5 to 7 days.

Cumulative nitrogen balance (grams)
n = 411, meta-analysis of 8 clinical trials (34)



Nitrogen balance explained



4 Versatile applications for sMLCT

In the USA, structured MLCTs are GRAS for use in medical foods. Extension of GRAS status to other applications is in preparation.

In Europe, structured MLCTs can be used in general foods, foods for special medical purposes, and infant formulas intended for specific therapeutic conditions; use in infant formulas for the general population has not been authorized.

In China, structured MLCTs have been approved as novel food.

Table 3

Food Category	Application	Typical sMLCT dose	Recommended total daily	Usage
Medical food or FSMP for children and adults with various health conditions (e.g. gastrointestinal conditions directly or indirectly affecting nutrition absorption)	Oral Nutritional Supplement (ONS)	6-9 g/237 ml	Max 1500 ml	As the sole source of nutrition or as supplemental nutrition
	Tube Feeding	6-9 g/237 ml	Max 1500 ml	
Powder milk or milk analogues	As such or reconstructed	3-7g/240ml	240ml	As supplemental nutrition, once per serving per day
Powder plant-based milk or milk analogues	As such or reconstructed	3-7 g/240 ml	240ml	As supplemental nutrition, once per serving per day
Milk-based drinks	Milk-based meal replacement	3-6g/330ml	330 ml	As supplemental nutrition, once per serving per day
Plant-based milk drinks	Plant-based milk meal replacement	3-6g/330ml	330ml	As supplemental nutrition, once per serving per day
Shakes or shakes substitutes (keto type)	Meal replacement shakes	9-16g/330ml	330ml	As supplemental nutrition, once per day
Adult supplements	Capsules	1,6g/capsule	3 capsules	As dietary supplement
	Liquid	15 g sMLCT oil	15 g	As dietary supplement

Disclaimer

This material is provided for information only. It is the responsibility of the manufacturer to ensure that use, dosage, and claims on consumer products are in conformity with local laws and regulations.

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