

GRAS Notice (GRN) No. 449

<http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/GRASListings/default.htm>

**ORIGINAL SUBMISSION**

# LEWIS & HARRISON

Consultants in Government Affairs

122 C Street, N.W., Suite 505  
Washington, D.C. 20001

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November 20, 2012

Office of Food Additive Safety  
Center for Food Additive Safety and Applied Nutrition  
Food & Drug Administration  
5100 Paint Branch Parkway  
College Park, MD 20740

Re: Notification of the GRAS Determination of Medium Chain Triglycerides When  
Added Directly to Human Food

Dear Sir or Madam:

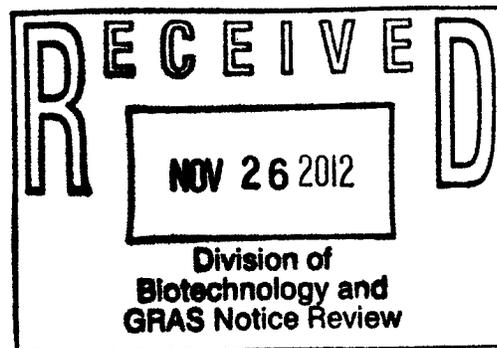
In accordance with proposed 21 CFR § 170.36(c)(1) (Notice of a claim for exemption based on a GRAS determination) published in the *Federal Register* (62 FR 18939-18964), I wish to notify you that Lonza Inc. has determined that medium chain triglycerides when added directly to food, under the conditions of use described below, will pose little or no risk from toxicity, and, therefore, are exempt from premarket approval requirements of the Federal Food Drug and Cosmetic Act (§ 409).

I am submitting the attached summary information, including the references upon which Lonza Inc. relied in making its GRAS determination. One original copy of this notice and a CD copy are enclosed.

Please let me know if you have any questions.

**Name and Address of Notifier**

Lonza Inc.  
attn: Robert Sloan  
90 Boroline Road  
Allendale, NJ 07401  
Telephone: (201) 316-9365  
Facsimile: (201) 696-3569  
e-mail: [bob.sloan@lonza.com](mailto:bob.sloan@lonza.com)



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Agent: Lewis & Harrison, LLC  
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### **Names and Identity of GRAS Substance**

Medium chain triglycerides (MCTs) are a class of lipids in which three saturated fats are bound to a glycerol backbone. MCTs are distinguished from other triglycerides in that each fat molecule is between six and twelve carbons in length. MCTs are a component of many foods, with coconut and palm oils being the dietary sources with the highest concentration of MCTs.

### **Applicable Conditions of Use**

Lonza has concluded that MCT is GRAS for the specific functional food types and uses listed below. The data evaluated in this GRAS Notification clearly shows that MCTs pose little or no risk from toxicity when consumed as a supplement in a balanced diet at levels up to 15% of the dietary calories or about 50% of the dietary fat.

- Food Types: Baked goods, beverages, chewing gum, confections and frostings, dairy product analogues, fats and oils, frozen dairy desserts, processed fruits, snack foods, adult nutritionals, cheeses and cheese spreads and soft candies.
- Functional Uses: Emulsifier, energy source, formulation aid, lubricant, release agent, nutrient supplement, processing aid, solvent, vehicle, stabilizer, thickener, surface finishing agent, and texturizer.

It should be noted that most of the uses noted above were the subject of a GRAS Affirmation Petition (GRASP 4G0409) that was previously submitted to FDA. Although the petition was filed by FDA, a regulation was never established pursuant to the petition due to resource limitations. However, it is Lonza's understanding the FDA did not object to the self-GRAS determination that served as the basis for GRASP 4G0409. This position is supported by FDA's response letter to GRAS Notice No. 217.

### **Basis for GRAS Determination**

Lonza's GRAS determination of MCTs is based upon well-established scientific procedures and upon scientific reviews of MCTs by a panel of qualified experts ("panel") assembled by Lonza in 2002 and 2003 and the review presented herein by Dr. Marcia van Gemert. Both the panel and Dr. van Gemert conducted an assessment of whether MCTs, when used in the food types noted above can be considered Generally Recognized as Safe (GRAS). The panel and Dr. van Gemert reviewed a large volume of clinical studies, toxicological studies, and other scientific information, as well as records of historical use, prior GRAS Notifications to FDA and foreign approvals.

The reviews by the panel and Dr. van Gemert concluded that:

- MCTs are sourced from a traditional food and have a safe history of use.
- MCTs and their component fatty acids have a very low acute toxicity in animals regardless of the route of administration.
- Studies in both experimental animals and humans indicate that MCT-based diets do not cause significant adverse health effects.
- MCTs administered in the diet have no adverse effect on rat reproduction or developmental parameters or on terminal gestational development and postnatal survival of pigs.
- There is no evidence of carcinogenicity in chronic studies.
- MCTs show little evidence of genotoxic or mutagenic potential.
- MCTs for the uses specified above can be considered GRAS.

### **Detailed Information Concerning the Identity of the Notified Substance**

#### **A. Identity**

MCTs are found naturally in milk-fat, including human breast milk (5-15%), palm oil and coconut oil and are obtained through lipid fractionation from coconut oil. In the 1950's MCTs were specially formulated as an alternative food source for very ill patients whose bodies could not properly digest normal fats and oils. At that time, MCTs were also used to reduce seizures with the help of the ketogenic diet. MCTs are metabolized differently from long chain fatty acids (LCTs). In LCT absorption, fatty acid chains are separated

from the glycerol backbone by the lipase enzyme. These fatty acids form micelles, are absorbed and reattached as glycerol, and the resultant triglycerides travel through the lymphatics to the bloodstream. MCTs have a unique metabolism, being preferentially

absorbed without the need for micelle formation, and they are transported by the portal vein to the liver for preferential oxidation. LCTs require large quantities of bile acids and

many digestive steps to be broken down into smaller units before they can be absorbed into the bloodstream. Once in the bloodstream, LCTs are absorbed by fat cells and stored as body fat. In contrast, the MCTs are more water soluble and are able to enter the bloodstream more quickly because of their shorter length. Once in the bloodstream, they are transported directly into the liver. Thus, MCTs are an immediately available source of energy and only a small percent is converted into body fat.

In the 1980s, MCTs became popular in the sports world as a substitute for normal fats or oils in the diet. They became a favorite energy source for many athletes who participate in endurance sports, such as marathon runners who require a quick source of energy, which can be readily supplied by carbohydrates. Diets high in carbohydrates, however, may cause a rapid increase in insulin production resulting in substantial weight gain, diabetes and other health problems. While dietary fats or oils are not a ready source of energy, MCTs provide a ready source of energy, do not cause weight gain, and are able to stimulate thermogenesis.

For over 30 years the special properties of MCTs have been utilized in human therapy. Examples of these properties include:

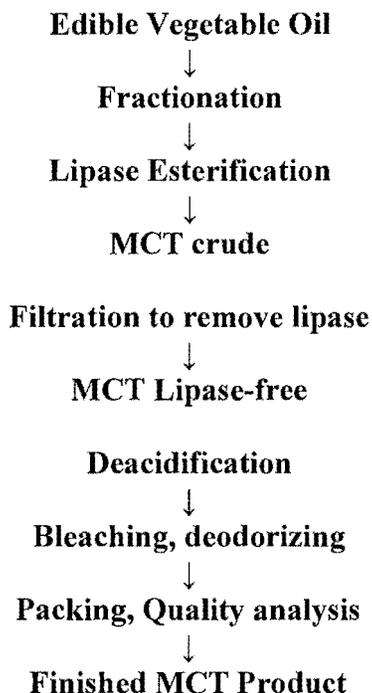
- MCTs are digested, absorbed and transported easily and rapidly in disorders where the digestion, absorption or transport of LCTs are not optimal.
- MCTs are oxidized rapidly in the organism and they have a very low tendency to deposit as body fat.
- MCTs are a source of abundant and rapidly available energy. MCTs are ketogenic.
- MCTs are donors of hydrogen ions and precursors of acetyl-CoA.
- MCTs are used as enteral and parenteral nutrition and appetite control, aiding in the prevention of obesity, or potentially stimulating weight loss.

## **B. Composition**

MCTs are a colorless or slightly yellowish, oily liquid, practically insoluble in water, and are miscible with alcohol, methylene chloride, light petroleum, and fatty oils.

MCTs are a unique class of lipids composed mainly of caprylic (C<sub>8</sub>; 50-80%) and capric fatty acids (C<sub>10</sub>; 20-50%) with a minor level of caproic (C<sub>6</sub>; 1-2%) and lauric (C<sub>12</sub>; 1-2%) fatty acids. They are derived from common edible oils rich in free medium chain fatty acids such as coconut or palm oil. Compositional analysis indicates that the fatty acids present are the type commonly found in other edible oils.

**C. Method of Manufacture of Medium Chain Triglycerides**



**D. Specifications for Food Grade MCT**

MCTs are manufactured in accordance with manufacturing control standards and the quality control standards of the International Organization for Standardization used at the Lonza Inc. manufacturing plant. All of the constituents of the subject MCTs are either approved food ingredients or are normal constituents found in commonly consumed foods at similar concentrations. The lipase has been deemed GRAS (21 CFR §184.1420), and is derived from a source organism considered safe.

**E. Self Limiting Levels of Use**

Due to its unique absorption characteristics, MCTs tend to be well tolerated, even in individuals with severe malabsorption. While fat malabsorption symptoms are generally fewer with MCTs than with LCTs, some steatorrhea can occur. Adverse symptoms are commonly described following a too large or not progressive enough incorporation in the diet of healthy volunteers or patients (Greenberger, *et al.*, 1969; Ruppin *et al.*, 1980; Rolls, 1988; Hopman, *et al.*, 1984; Seaton, *et al.*, 1986; Eckel, *et al.*, 1992; Bergen *et al.*, 1966; Holt, 1967). These symptoms can include nausea, vomiting, bloating, emesis,

gastrointestinal discomfort, abdominal cramps, and osmotic diarrhea. In a 91-day dog study dogs fed up to 15% MCT in their diets showed no safety concerns but had some palatability issues with the feed, indicating a possible self-limiting effect of MCTs (Matulka, *et al.*, 2009).

#### **F. GRAS Exemption Claim**

Employing scientific procedures established under 21 CFR § 170.30 (b) and based on scientific data reviewed by the panel and Dr. Marcia van Germert, Lonza have determined that medium chain triglycerides, when used directly in food for the uses detailed above, are GRAS.

The attached GRAS Determination Dossier provides detailed information about the identity of the GRAS substance, including chemical name, Chemical Abstracts Service Registry Numbers, empirical formulas, quantitative composition, method of manufacture, characteristic properties, and summaries of pertinent safety information (metabolism and toxicology studies). The attached GRAS dossier also contains a detailed summary of the basis for Lonza's determination that the particular uses of the notified substance are exempt from the premarket approval requirements of the Federal Food, Drug and Cosmetic Act ("FFDCA") because the uses are GRAS.

#### **Availability of Information:**

The data and information that are the basis for this GRAS determination are available for FDA to review and copy at reasonable times at the offices of Eliot Harrison, Lewis & Harrison, 122 C St. N.W., Suite 505, Washington, D.C. 20001.

Telephone: (202) 393-3903, ext. 14.  
Facsimile: 202-393-3906  
E-Mail: [eharrison@lewisharrison.com](mailto:eharrison@lewisharrison.com)

Alternatively, copies of data and information can be provided to FDA upon request, by contacting Mr. Harrison.

Sincerely yours,

(b) (6)

Eliot Harrison  
Lewis & Harrison LLC  
Agent for Lonza Inc.

**SUBJECT:**

GENERALLY RECOGNIZED AS SAFE DETERMINATION  
FOR MEDIUM-CHAIN TRIGLYCERIDES WHEN ADDED  
DIRECTLY TO HUMAN FOOD

**NOTIFER:**

Lonza Inc.  
Allendale, N.J.

**DATE:**

November 20, 2012

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## 1. GRAS EXEMPTION CLAIM

Lonza Inc. is filing this GRAS Notification to:

Office of Food Additive Safety (HFS-255)  
Center for Food Safety and Applied Nutrition  
Food & Drug Administration  
5100 Paint Branch Parkway  
College Park, MD 20740

The use of medium-chain triglycerides (MCTs), when added to food directly, is exempt from premarket approval requirements of the Federal Food, Drug, and Cosmetic Act (“FFDCA”) because the notifier has determined that such use is GRAS.

### (i) Notifier

Lonza Inc.  
attn: Robert Sloan  
90 Boroline Road  
Allendale, NJ 07401  
Telephone: (201) 316-9365  
Facsimile: (201) 696-3569  
e-mail: [bob.sloan@lonza.com](mailto:bob.sloan@lonza.com)

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e-mail: [eharrison@lewisharrison.com](mailto:eharrison@lewisharrison.com)

### (ii) Name of GRAS Substance

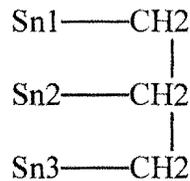
Medium Chain Triglycerides (MCTs), CAS No. 73398-61-5

MCTs are a colorless or slightly yellowish, oily liquid, practically insoluble in water, and is miscible with alcohol, methylene chloride, light petroleum and fatty oils.

MCTs are a unique class of lipids that are composed mainly of caprylic (C<sub>8</sub>; 50-80%) and capric fatty acids (C<sub>10</sub>; 20-50%) with a minor level of caproic (C<sub>6</sub>; 1-2%) and lauric (C<sub>12</sub>; 1-2%) fatty acids. They are derived from common edible oils rich in free medium chain fatty acids, such as coconut or palm oil. Compositional analysis indicates that the fatty acids present are the type commonly found in other edible oils.

MCTs are edible oils composed of a glycerol backbone with medium chain fatty acids randomly bound to the Sn1, Sn2 or Sn3 positions (refer to Figure 1 below).

**Figure 1: Chemical structure of a triglyceride backbone. Sn1, Sn2, and Sn3 refer to the positions for the three fatty acid molecules to attached to the triacylglycerol backbone (Babayán, 1987).**



MCTs are edible oils and are components of many foods, produced from coconut and palm oil kernel oils. MCTs are produced conventionally by splitting and distilling the extracted fatty acids, mixing them to the desired ratio, and esterifying with glycerine to form a triglyceride.

### **(iii) Conditions of Use**

Lonza has concluded that MCTs are GRAS as a direct food ingredient for the specific functional uses and food types listed below. The data evaluated in this GRAS Notification clearly demonstrate that MCTs would pose little or no dietary risks when consumed as a supplement in a balanced diet at levels up to 15% of the dietary calories or about 50% of the dietary fat.

- Food Types: Baked goods, beverages, chewing gum, confections and frostings, dairy product analogues, fats and oils, frozen dairy desserts, processed fruits, snack foods, adult nutritionals, cheeses and cheese spreads and soft candies.
- Functional Uses: Emulsifier, energy source, formulation aid, lubricant, release agent, nutrient supplement, processing aid, solvent, vehicle, stabilizer, thickener, surface finishing agent, and texturizer.

#### **(iv) Basis for GRAS Determination**

Lonza's GRAS determination of MCTs is based upon well-established scientific procedures and upon scientific reviews of the MCTs by a panel of qualified experts ("panel") assembled by Lonza in 2002 and 2003 and by a separate scientific evaluation conducted by Dr. Marcia van Gemert. Dr. van Gemert is a noted toxicologist with over 30 years of experience in evaluating the safety of food substances. Both the panel and Dr. van Gemert conducted an assessment of whether MCTs, when used in the food types noted, above can be considered as Generally Recognized as Safe (GRAS).

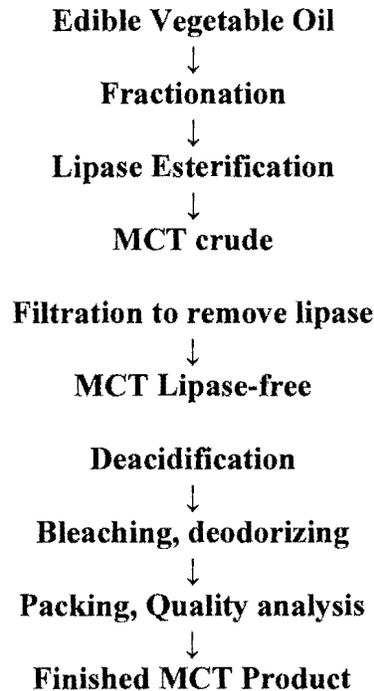
The panel and Dr. van Gemert reviewed a large volume of clinical studies, toxicological studies, and other scientific information, as well as records of historical use, prior GRAS Notifications to FDA, and foreign approvals. The review concluded that:

- MCTs are sourced from a traditional food and have a safe history of use.
- MCTs and their component fatty acids have a very low acute toxicity in animals regardless of the route of administration.
- Studies in both experimental animals and humans indicate that MCT-based diets do not cause significant adverse health effects.
- MCTs administered in the diet have no adverse effect on rat reproduction or developmental parameters or on terminal gestational development and postnatal survival of pigs.
- There is no evidence of carcinogenicity in chronic studies.
- MCTs show little evidence of genotoxic or mutagenic potential.
- MCTs for the uses specified above can be considered GRAS.

## **2. Description, Manufacturing Process and Specifications**

The MCTs are an edible vegetable oil manufactured from common edible vegetable oils containing medium and long chain fatty acids. The most common source of MCTs is from coconut and/or palm kernel oil. These edible oils are fractionated and then combined with a lipase utilized to promote a randomized ester exchange. The crude MCTs are then filtered to remove the lipase, deacidified, bleached, and deodorized resulting in the finished MCT product.

**(i). Method of Manufacture of Medium-Chain Triglycerides**



**Figure 2. Medium Chain Triglyceride Production Scheme**

MCTs are manufactured in accordance with manufacturing control standards and the quality control standards of the International Organization for Standardization used at the Lonza Inc. manufacturing plant. All of the constituents of the subject MCTs are either approved food ingredients or are normal constituents found in commonly consumed foods at similar concentrations. The lipase has been deemed GRAS and is derived from a source organism considered safe.

The starting materials (i.e., common vegetable-coconut or palm kernel oil) are produced by traditional manufacturing methods, which include saponification or hydrolysis that produces mixed fatty acids. The fatty acid mixture is subjected to fractional distillation to isolate the medium chain fatty acids (MCFAs). The MCFAs are esterified with glycerin to produce a crude MCTs product, which is purified using traditional oil processing procedures.

Esterification is initiated by allowing the vegetable oils (MCFAs as raw material) to be exposed to the lipase. The crude oil product is filtered to remove lipase. Then the product is subjected to traditional oil processing (i.e., de-acidification, bleaching, deodorizing, mixing, packing and analysis) to produce the final MCT product. The MCT product is washed with hot water during the de-acidification process, ensuring the complete removal of lipase from the product.

## **(ii). Specifications for MCT**

### **Product Information, Lonza Group**

The product is MCT- Medium Chain Triglycerides.

Kosher Food Grade

Fractionated Coconut Oil Ester

CAS No. 73398-61-5

INCI Designation: Caprylic/Capric Triglyceride

<b><u>Specifications</u></b>	<b><u>UOM</u></b>	
Hydroxyl Value	%	10% Max.
Saponification Value	SV	320-340
Color Lovibond, Red	LOV	0.25 Max.
Free Fatty Acid	Mileq	0.50 Max.
Water content	%	0.05 Max.
Peroxide Value	Mileq	1.0 Max.
Iodine Value	IV	0.1 Max.
Viscosity @ 100F	CPS	
C6 Content	%	0.5 Max.
C8 Content	%	53.0-57.0
C10 Content	%	42.0-46.0
C12 Content	%	1.5 Max.

### **Typical Properties**

Appearance	Clear liquid
Odor	Neutral
Taste	Neutral

## **3. Dietary Intake**

Recent subchronic studies in humans have provided confirmation of earlier dietary studies and show that MCTs exhibit very low toxicity when administered in the diet at levels up to 15% of the diet. MCT-based diets have been shown to cause minor alterations in serum lipid profiles, which have occasionally translated into slower rates of weight gain relative to long-chain triglyceride-based diets (Traul, *et al.*, 2000).

Many studies in humans that will be discussed in detail in this notification estimate that MCTs have typically been used in diets for children at 15-30 gm/day, and 40-100 gm/day in adults, covering up to 40% of the daily energy requirements (Bach, *et al.*, 1996).

Studies of MCTs carried out recently (Chanez, 1991; Webb, 1993) are consistent with regard to the observations that MCTs can be administered by various routes at relatively high dose levels, especially in the diet or by oral gavage, without significant adverse effects. NOAEL values from dietary studies appear to be consistently of the order of

3000-5000 mg/kg body weight/day and have been reported as high as 12,000 mg/kg body weight/day. A standard 2500 cal/day diet, in which 30% of the dietary calories is fat (Traul *et al.*, 2000) would include about 83.3 gms of fat/day. If 15% of the dietary calories, or 50% fat, were MCTs, the daily dietary intake of MCTs would be 41.7 gms/day. For a 60-kg individual, that would be about 0.7 g/kg body weight/day MCT (Traul, *et al.*, 2000).

#### **(i). Self-limitation of use of medium-chain triglyceride**

Due to its unique absorption characteristics, MCTs tend to be well tolerated, even in individuals with severe malabsorption. While fat malabsorption symptoms are generally fewer with MCTs than with LCTs, some steatorrhea can occur. Adverse symptoms are commonly described following a too large or not progressive enough incorporation in the diet of healthy volunteers or patients (Greenberger, *et al.*, 1969; Ruppin *et al.*, 1980; Rolls, 1988; Hopman, *et al.*, 1984; Seaton, *et al.*, 1986; Eckel, *et al.*, 1992; Bergen *et al.*, 1966; Holt, 1967). These symptoms can include nausea, vomiting, bloating, emesis, gastrointestinal discomfort, abdominal cramps, and osmotic diarrhea. In a 91-day dog study dogs fed up to 15% MCT in their diets showed no safety concerns but had some palatability issues with the feed, indicating a possible self-limiting effect of MCTs (Matulka, *et al.*, 2009).

### **4. Absorption, Distribution, Metabolism and Elimination (ADME)**

Upon ingestion, MCTs are partially hydrolyzed to medium chain fatty acids (MCFAs) by buccal, lingual, gastric, intestinal, and pancreatic lipases in the stomach, and then completely broken down by pancreatic lipase inside the intestinal lumen to form free fatty acids and glycerol. MCFAs are more hydrophilic than long chain fatty acids (LCFAs), the majority of MCFA do not require micelle-containing bile salts or chylomicron formation, but are directly absorbed into the liver via the portal vein rather than through the thoracic duct lymph system that is the conventional route for the absorption of triglycerides containing long-chain fatty acids. A minor fraction of MCFAs bypass the liver and are distributed to peripheral tissues via the general circulation (Babayan, 1988; Bach and Babayan, 1982; Traul, *et al.*, 2000). The MCFAs are catabolized predominantly in the liver to C<sub>2</sub> fragments such as acyl CoA esters. The C<sub>2</sub> fragments are further converted to CO<sub>2</sub>, or used to synthesize longer-chain fatty acids. Very little of the MCT, if any, is stored in adipose tissues (Greenberger and Skillman, 1969; Traul *et al.*, 2000). Medium chain fatty acyl CoAs (mainly of caprylic and capric acids), in the hepatocytes, are transported across the mitochondrial membrane via a carnitine-independent mechanism. Once in the mitochondria, they are metabolized, initially by medium-chain acyl CoA dehydrogenase, to acetoacetate and beta-hydroxybutyrate (Schwab *et al.*, 1964; Babayan, 1987; Bell *et al.*, 1997). Acetoacetate and beta-hydroxybutyrate may be further metabolized in the liver to CO<sub>2</sub>, water and energy, and may enter other metabolic pathways in the liver or be transported by the systemic circulation to other tissues, where they are metabolized to produce CO<sub>2</sub>,

water and energy. Studies with adult human volunteers have shown that little, if any, of the MCT is stored in adipose tissue (Bach *et al.*, 1996).

In contrast, LCTs are converted to LCFAs (e.g. C16-C18, which are the primary fatty acids in dairy meat and vegetable oil fat) and monoacylglycerol in the intestinal lumen. These are incorporated into chylomicrons and absorbed via the lymphatic system. Chylomicrons eventually reach the general circulation and are distributed to extrahepatic tissues where they are metabolized into LCFAs by the action of lipoprotein lipase. The resulting 'free' LCFAs reach the liver via the systemic circulation. In the presence of pancreatic lipase or bile salt deficiency, MCTs can still be absorbed whereas LCTs cannot (Bach and Babayan, 1982). They also have a carnitine-independent entry into mitochondria and undergo rapid  $\beta$ -oxidation to furnish energy for the cell (Babayan, 1987; Greenberger and Skillman, 1969; Traul *et al.*, 2000). Consequently, the MCTs are used extensively in human nutrition as a source of energy for individuals with malabsorption syndromes and for total parenteral nutrition (Traul, *et al.*, 2000).

The hepatic mitochondrial metabolism of MCFAs such as caprylic and capric acid ultimately results in an excess of acetyl-CoA that in turn results in the production of acetate, CO<sub>2</sub> and ketone bodies, with a minor portion serving to lengthen endogenous fatty acids (Bach and Babayan, 1982). However, some investigators have suggested that MCT diets, when fed in excess of caloric needs, might lead to increased *de novo* fatty acid synthesis and enhanced fatty acid elongation activity in the liver (Hill *et al.*, 1990). Most of the MCFAs are catabolized within the liver with only a minor portion reaching the general circulation bound to albumin.

Although consumption of MCTs can lead to ketone production, it is generally accepted that there is no risk of ketoacidosis or ketonaemia with MCTs at levels associated with normal consumption levels. High circulating levels of caprylic acid can cause central nervous system toxicity (coma), however these concentrations are not achieved from consuming MCTs, even at levels higher than would normally be found in food products (e.g. about 10-15% in baked goods (Bach and Babayan 1982; Bach *et al.*, 1977).

MCT-based diets have been shown to cause minor alterations in serum lipid profiles, and have infrequently produced slower rates of weight gain relative to long chain triglycerides-based diets. Experimental studies in both animals and humans have shown that MCT-based diets do not cause significant toxicity, even when the diets have consisted of more than 5% MCTs (Traul *et al.*, 2000). In low birth-weight infants, MCTs have been shown to improve fat absorption without significantly changing body weight. Nutritional studies have concluded that:

- (1) MCTs are calorically less dense than LCTs;
- (2) the energy retention of MCT-based diets is less than that of LCT-based diets; and
- (3) the thermic response to food is greater after an MCT-based meal.

None of these attributes are considered clinically adverse. Clinical trials have indicated that normal dietary levels of MCTs have no significant effect on the absorption of vitamins A, D, or E. Furthermore, there are no adverse effects on mineral absorption or retention of minerals such as calcium, magnesium or phosphorus (Traul, *et al.*, 2000).

## **5. Safety Evaluation**

MCTs have been evaluated in acute, subchronic, chronic, reproductive, developmental and genotoxicity studies using the oral, dermal, intraperitoneal, inhalation or intramuscular routes of administration. For this GRAS notification, only the oral studies will be considered. The oral mammalian toxicology studies reported used as an MCT source Neobee M-5 or Miglyol 812 for the toxicity studies. Additionally, some studies are included below in which the products are identified only as medium-chain triglycerides (MCTs) or caprylic/capric triglycerides, which share the general specifications for Neobee M-5 and Miglyol 812.

### **(i) Acute Studies**

The acute oral toxicity of MCTs (caprylic/capric triglyceride) has been evaluated in eight single dose studies in the mouse and the rat. In these studies doses between 4.5 ml/kg and 36 ml/kg did not produce mortality. The LD<sub>50</sub> was not established, but is greater than 25 ml/kg (mice) or 36 ml/kg (rat) (Traul, *et al.*, 2000).

In a mouse study, Tyler's Original strain mice were treated with 5.0, 10.0, 20.0 and 25.0 ml/kg Miglyol 812 in a range-finding study with no deaths. In the definitive study conducted with 25 ml/kg, lethargy and ataxia occurred within 10 minutes after administration of 25 ml/kg and dyspnea was noted in some animals within 1 hour, but not thereafter. All animals appeared asymptomatic at the end of the first day. No necropsy observations were reported (Poole, 1977; Traul, *et al.*, 2000).

Another mouse study tested Miglyol 810 (slightly higher portion of C<sub>8</sub> fatty acids than Miglyol 812) at 12.5, 20.0 and 25.0 ml/kg. Transient ataxia, lethargy, dispnea and diuresis occurred within 15 minutes in the mid- and high-dose groups, and complete loss of activity was observed within 2 hours, followed by recovery, in several animals in the high dose. Deaths occurred within 24 to 48 hours in two animals that received 20 ml/kg and one animal that received 25 ml/kg. All symptoms disappeared in the survivors by the end of day 3. No necropsy observations were reported (Poole, 1977; Traul, *et al.*, 2000).

Miglyol 812 was evaluated in fasted Wistar male rats, where a single dose from 4.5 to 36 ml/kg produced no toxic effect during the 10-day observation period or at necropsy. The only observation was that the animals receiving 18 and 36 ml/kg consumed less feed and excreted softer feces for the first 2 days (Klimmer, 1971; Traul, *et al.*, 2000).

In each of four single dose acute studies, five male and five female Wistar rats were given 5 g/kg Miglyol 812 and observed for 14 days. No deaths, adverse observations or abnormal gross pathology findings at necropsy were noted (Anonymous, 1977; Lewis and Palanker, 1977; Palanker, 1976a,b; Traul, *et al.*, 2000).

Acute oral toxicity studies have also been carried out in rodents with constituent medium-chain fatty acids.

A study involving groups of 10 young adult Osborne-Mendel rats established that the oral LD<sub>50</sub> for caprylic acid was 10,080 mg/kg (Jenner *et al.*, 1964). In this study, rats were evenly divided by sex and were fasted for approximately 18 hours prior to treatment by intubation. Rats were allowed access to food and water *ad libitum* post-treatment. The only indications of toxicity noted by the investigators in surviving animals were depression and diarrhea.

A study carried out in rats by Smyth *et al.*, (1962) determined that the oral LD<sub>50</sub> in rats was 1.41 ml/kg and 3.73 ml/kg for caprylic and capric acid, respectively.

The acute toxicity of several mixed preparations of caprylic/capric acid triglyceride has also been investigated in a series of oral studies in mice and rats (Elder, 1980). This series of studies indicated that the oral LD<sub>50</sub> for female mice was greater than 25 ml/kg. In the first mouse study, at a dose of 25 ml/kg, lethargy and ataxia were observed within 10 minutes of administration, and dyspnea within 1 hour. 24 hours after administration, all animals appeared asymptomatic and survival was 100%. In the second mouse study, using dose ranges from 12.5 to 25 ml/kg, ataxia, lethargy and dyspnea were noted within 15 minutes, which progressed to a complete loss of activity in a few animals by 1 hour. At doses of 20 and 25 ml/kg, three deaths out of 15 animals occurred within 48 hours (20% mortality); surviving animals were asymptomatic by 72 hours (Traul, *et al.*, 2000).

In the same series of oral toxicity studies (Elder, 1980), the oral LD<sub>50</sub> for male rats was determined to be greater than 36 ml/kg. Doses of 18 and 36 ml/kg did not result in any mortality and there were no significant findings reported at necropsy on day 11. A second study involving both male and female rats concluded that the LD<sub>50</sub> of four other mixed preparations of caprylic/capric triglyceride was greater than 5000 mg/kg.

## **(ii) Subchronic Toxicity Studies**

A 3-week dietary study in chicks was performed using Miglyol 812 incorporated into the diet at a level of 16% and fed to 12, 7-day-old Single comb White Leghorn male chicks for three weeks. A control group received standard diet. The treated group had reduced body weight gain, ruffled feathers and reduced muscle weight. These effects were due to the reduced feed consumption by chicks receiving the high fat diet. All mortality was due to starvation and not the consumption of Miglyol 812. The absence of "chick oedema factor" was determined by the absence of hydropericardium, hydroperitoneum and subcutaneous edema at the time of autopsy.

Gross autopsy did not reveal any abnormal liver or kidney changes. The results of this study showed that Miglyol 812 did not contain chick edema factor and that Miglyol is not toxic to chicks (Roth and Shapiro, 1981; Traul *et al.*, 2000).

In two separate tests, groups of 10 male Wistar rats were given either 1 or 3 ml MCT (Miglyol 812) by oral gavage for 30 days. This represented doses ranging from 3.58 to 7.56 ml/kg. body weight/day or 10.8 to 21.3 ml/kg/body weight/day, respectively over the course of the studies. No toxic effects or adverse effects on weight gain or urinalysis values were noted, although during the first 5-7 days of the trial there were transitory reductions in food intake and other digestive disturbances, such as diarrhea (Klimmer, 1971; Traul, *et al.*, 2000).

Groups of 20/sex rats were fed MCT (Miglyol 812) at 0, 10,000 or 50,000 ppm in the diet (representing 0, 1% and 5% of the diet) for 3 months. There were no reported signs of toxicity and no reported adverse effects on body weight, body weight gain, blood chemistry values or organ weights. The blood chemistry included measurements of liver enzymes AST and ALT and non-esterified fatty acids and esterified fatty acids, which were all within normal range. This study showed that feeding Miglyol 812 did not increase triglyceride levels or induce a hyperlipidemic condition. At necropsy, absolute and brain-weight-relative weights of the liver, kidney, adrenal gland, thyroid gland, gonads and brain of the rats fed test material were not different from controls. The no-observed-adverse-effect level (NOAEL) for this study was determined to be greater than 50,000 ppm in the diet (Klimmer, 1971; Traul, *et al.*, 2000).

Groups of 25/sex weanling Crl:CD BR Sprague-Dawley rats were fed caprenin at 0, 5.23, 10.23 or 15.00% in the diet for 91 days. Caprenin is a mixed-chain MCT/LCT consisting of caprylic (23.2%), capric (26.6%), and behenic (C<sub>22</sub>, 45%). Control animals were fed diets of corn oil (12.1%) or a mixture of corn oil and Captex 300, an MCT (3.1% and 11.21%, respectively). All diets contained at least 3% corn oil to provide essential fatty acids and were balanced at about 4000 kcal/kg and provided 26.8% of daily calories as fat, 19.4% as protein and 52.4% as carbohydrate.

The test groups showed no treatment-related deaths and clinical observations showed no significant differences in body weights or body weight gains across all groups. There were no gross or histopathological findings and no significant differences between groups in the total fat content of the hearts, livers or peripheral fat pads. However, there was a trend to lower amounts of fat deposited in the animals fed caprenin-containing diets. The NOAEL for caprenin was determined to be equal to or greater than 15% of the diet (approximately 13.84 and 15.3ml/kg body weight/day for males and females, respectively) and for MCTs, in the corn oil/MCT diet, to be greater than 11.2% of the diet (approximately 9.6 ml/kg body weight/day) (Webb, *et al.*, 1993; Traul, *et al.*, 2000).

Many subchronic studies that have been carried out with MCTs in laboratory animals and in humans were designed to compare MCT- with LCT-containing diets. In the accounts of these studies, the effect of an MCT-based diet on the endpoint of interest (degree of fat deposition) is reported relative to the effect or response observed after feeding an LCT-based diet.

In a 6-week study, no significant adverse effects were observed when 15 male Sprague-Dawley rats were fed, via oral intubation, either an MCT- or an LCT-containing diet that derived 50% of the calories from fat. Animals fed the MCT diet had significantly lower levels of dissectable fat, which was attributed to higher resting and maximal norepinephrine-stimulated O<sub>2</sub> consumption and metabolic rate. Liver fat and blood glucose values were comparable between the two groups (Baba, *et al.*, 1982).

In a similar 6-week study in which male Sprague-Dawley rats were fed, via oral intubation, an MCT or LCT diet which derived 50% of the calories from fat, the MCT-fed rats gained 20% less weight and had fat deposits weighing 23% less than LCT-fed rats. Over the course of the study, rats were monitored for total spontaneous physical activity over a 24-hour period, and no differences between the two groups were noted, suggesting that MCTs do not induce overt toxicity as would be suggested by the absence of lethargy. Serum insulin levels and the weights of carcass protein and water were not different between the two groups (Geleibter, *et al.*, 1983; Traul, *et al.*, 2000).

In a 45-day study using male Wistar CF rats, the test animals were fed fat-containing diets. 32% of the metabolizable energy was constituted by LCTs or MCTs. The data showed that rats fed the MCT diet had depressed levels of serum cholesterol, weight gain was decreased by 21% and energy retention was decreased by 26% relative to the LCT-fed rats. The LCT diet increased lipid deposition 1.5-1.7 fold. No significant differences were noted between the LCT and MCT groups with respect to plasma glucose, triglycerides, free fatty acids or liver weight; hepatic glycogen levels were 50% lower in the LCT group (Chanez, *et al.*, 1991).

In a recent 90-day feeding study in beagle dogs MCT was fed at levels of 0%, 5%, 10% and 15% MCT added to conventional feed. The beagles were monitored for signs of toxicity by clinical observations, body weight measurements, food consumption levels, physical examinations, hematology and serum chemistry, ophthalmic examinations, and urinalysis. There were no signs of toxic effects observed in any of the animals that were related to feed, and the animal viability was 100% at the end of the study. Some animals exhibited significant increased blood urea nitrogen, potassium and cholesterol levels in the 10% and 15% MCT-fed groups. Also, in the same groups with elevated nitrogen, there were concomitant reductions in total blood protein and urine volumes. These changes in serum chemistry may be the result of protein sparing effects due to the high levels of MCT intake, and are not deemed to be pathological in nature.

Animals receiving 15% MCT in feed had lower levels of food intake due to palatability issues. From the other examination parameters, there were no significant changes noted between groups receiving MCT and vehicle feed. No safety concerns were noted at any dose level, although an issue with palatability precluded identifying 15% as the highest dose level tested (Matulka, *et al.*, (2009).

### **(iii) Reproduction and Developmental Studies**

In a reproduction study, Sherman albino rats were fed diets containing 20% of either lard or MCT in addition to 0.09% linoleic acid for 10-12 months. No effect on fertility was noted (Kaunitz, *et al.*, 1958). In another reproduction study, young adult male and female Wistar rats were fed a balanced diet containing 19.6% of an MCT of 75% caprylic and 25% capric acid for 3 weeks before mating. This group was compared to concurrent groups fed high oleo oil, butterfat or coconut oil diets. A third reproduction study was conducted to determine whether feeding MCTs to sows during late gestation and early lactation would improve neonatal survival. Beginning on day 91 of gestation and continuing through day 7 of lactation, three groups of sows were fed either isoenergetic (7000 kcal metabolizable energy/day) and isonitrogenous (278 gms crude protein/day) amounts of either control (19% starch, 2% soybean oil), long chain triglycerides (LCT, soybean oil, 12%) or MCT (10% MCT, 2% soybean oil) diets. The results suggest that not only is survival improved, but that certain reproductive parameters, such as litter size, live births, birth weights and litter survival during early lactation and late lactation, are not adversely affected by dietary administration of MCTs (Azim, 1993; Traul, *et al.*, 2000). The results of these three studies indicated that MCTs administered in the diet had no adverse effect on rat reproductive or developmental parameters or on terminal gestational development and postnatal survival of pigs.

### **(iv) Chronic Toxicity/Carcinogenicity Studies**

In a study in which Sherman albino rats were fed diets containing 20% of either lard or MCT in addition to 0.09% linoleic acid for 10 to 12 months, no overt toxicity was observed and there was no difference in survival between the two groups. Rats fed MCT gained approximately 15% less weight during the study. This difference was shown not to be the result of fecal fat losses. A second component of the study involved the comparison of serum cholesterol levels in rats fed the lard-based diet vs. the MCT-based diet supplemented with either 0, 0.09 or 2% linoleic acid. Rats fed the MCT diet had serum cholesterol levels that ranged from 55 to 76 mg vs. 83 to 129 mg for rats on the lard diet. The rats fed diets with 0.09% linoleic exhibited greater caloric requirements than the groups fed diets containing 2.0% linoleic acid or lard. There were no adverse toxicological effects reported for animals fed diets containing MCT (Kaunitz, *et al.*, 1958; Traul, *et al.*, 2000).

The chronic toxicity profile of MCTs was evaluated in a dietary study involving 15/sex Wistar rats. The rats were fed diets that differed only with respect to the source of dietary fat that supplied 40% of the total calories (21% fat). The fats tested were MCT (approximately 75% caprylic and 25% capric acids), oleo oil, butterfat and coconut oil to which 2.5% safflower oil was added to ensure adequacy of the essential fatty acids in all diets. The study was for 47 weeks. The consumption of MCT was approximately 9 gms/kg body weight/day. The results showed that the MCT diet supported normal growth and development and there was no difference in mortality between the various treatment groups. Organ weights of the liver, kidney, spleen, heart, adrenals, and testes were similar in all groups at the end of the study, and histological examination of the liver and intestine showed no marked difference. At the end of 47 weeks, mean weight gain for rats fed the MCT diet was equivalent to those recorded for all other diets, but significantly less than that observed in rats fed the coconut oil based diet (Harkin and Sarett, 1968; Traul, et al., 2000).

The National Toxicology Program (NTP) tested tricaprylin, a triglyceride in which all three fatty acids are C<sub>8</sub>, (caprylic acid) in a 2-year chronic toxicity and carcinogenicity study. In this study, male F344/N rats were gavaged with 0, 2.5, 5 or 10 ml tricaprylin/kg body weight daily, 5 days/week for 2 years.

The 2-year survival of the high dose tricaprylin male rats was lower than that of the control rats (0 mg/kg- 31/50; 2.5 ml/kg-30/50; 5 ml/kg- 31/50; 10 ml/kg- 23/53) due to moribund kills and deaths that appeared to be related to toxicity. The mean body weight of the high dose group was lower than that of the controls throughout the study, although the difference was less than 5% after week 61.

There was a significant dose-related increased incidence of pancreatic exocrine hyperplasia and adenoma (hyperplasia: 8/49, 9/49, 18/49, 28/50; adenoma: 2/49, 6/49/ 13/49/ 18/50). The incidence of proliferative lesions of the forestomach increased significantly with dose (basal cell hyperplasia: 4/50, 7/50, 12/49, 21/52: squamous cell papilloma: 0/50, 0/50, 3/50, 10/53). There were no significant increases in carcinomas found in this study (NTP, 1994; Traul, et al., 2000).

The results of these chronic studies are consistent with the findings of the acute and subchronic studies and suggest that MCTs have very low toxicity. These studies also suggest that the route of administration (dietary vs oral gavage) may influence the apparent toxicity of MCTs during chronic administration (Traul, et al., 2000).

#### **(v) Genotoxicity Studies**

Caprylic acid exhibited no mutagenic activity in microbial mutation assays with and without metabolic activation. The indicator organisms were *Saccharomyces cerevisiae* strain D4 and *Salmonella typhimurium* strains TA1535, TA1537, and TA1538 (Brusick, 1976).

NTP tested tricaprylin for mutagenic activity in the Ames mutagenicity plate incorporation assay with and without metabolic activation. Tricaprylin was mutagenic in strain TA1535 with, but not without S9 activation. Tricaprylin did not induce mutations in strains TA97, TA98, or TA100 with or without S9 activation (NTP, 1994).

According to the review by Traul, *et al.*, (2000) the evidence for the genotoxicity of MCTs is weak. Tricaprylin was not classified as a carcinogen in the chronic carcinogenicity study and caprylic acid was not mutagenic in yeast or bacteria. The positive result with tricaprylin in one strain of bacteria in the Ames test does not appear to suggest that tricaprylin should be classified as a mutagen.

#### **(vi) Clinical Studies**

Human clinical studies have also been reported using MCTs as a fat source. A study was conducted with eight patients who were fed formula diets containing either MCTs (77.7% C<sub>8</sub> (caprylic), 19.6% C<sub>10</sub> (capric), 1.9% C<sub>6</sub> and 0.8% C<sub>12</sub>), butter or corn oil as sole isocaloric source of dietary fat. The study lasted up to 10 weeks and used a crossover study design; each formula derived 40% of its caloric content from fat. The MCT- and corn oil-containing diets were shown to produce significantly lower cholesterol levels, relative to steady-state levels achieved on the butter diet. The only side effect documented for the MCT formula was a transient period of nausea and abdominal fullness during the first 3-4 days (Hashim, *et al.*, 1960; Traul, *et al.*, 2000).

In another human study, four human volunteers who had been fasted overnight were fed 1 gm MCT/kg body weight (71% caprylic, 15% capric, 3% lauric). Their serum-free fatty acids showed a high proportion of octanoic acid and a low proportion of long-chain acids for 4 hours after feeding the MCT preparation. No toxicologic symptoms were reported (Ender, 1980; Traul, *et al.*, 2000).

When 10 human volunteers ingested 1000 ml (approximately 95 grams) of synthetic fat (a triglyceride of 74% lauric, 17% capric, 5% caprylic, 3% myristic, and a trace of caproic) eight had no chylomicrons in their sera, and none developed diarrhea or had fat in their feces. All had increased levels of free fatty acids in their sera. These results support other data that show that MCTs are readily metabolized in the intestine and are absorbed primarily as free fatty acids without adverse effects (Ender, 1980; Traul, *et al.*, 2000).

In another study, 10 non-obese males were over-fed (150% of estimated energy requirements) two formula diets for 6 days each, in a randomized crossover design. The fat component of the diets represented 40% of caloric energy either as MCT or LCT. No significant clinical toxicity was reported. In contrast to the reports cited above, a reduction in fasting serum total cholesterol was noted for the LCT diet but not for the MCT diet. A three-fold increase in fasting serum triglyceride values was noted for the MCT, but not for the LCT diet.

It was suggested that MCT diets, when fed in excess of caloric needs, might lead to increased *de novo* fatty acid synthesis and enhanced fatty acid elongation in the liver (Hill *et al.*, 1990; Traul, *et al.*, 2000).

A number of studies in humans have been reported concerning some of the potentially beneficial aspects of MCTs, such as use as a component for enhanced weight loss programs, increased energy during exercise, fat malabsorption states, cystic fibrosis, epilepsy, and diabetes. Although most of these studies do not directly examine the toxicological safety of MCTs, and are not going to be considered in this GRAS notification, they do document the widespread safe historical consumption of MCTs.

#### **(vii) Sensitive Populations**

Fat malabsorption sufficient to contribute to malnutrition is common in cirrhosis (Linscheer *et al.*, 1966). In a clinical study designed to evaluate the incidence of fat malabsorption in patients with alcoholic cirrhosis, a group of 10 patients were given equicaloric MCT or LCT liquid diets in alternating periods of 6 days. The absorption of MCTs was found to be significantly better than of LCTs, as determined from stool fat measurements. In the same study, the absorption of caprylic acid after infusion into the upper small bowel was compared between control and cirrhotic patients. An analysis of plasma caprylic acid concentrations demonstrated that although there were comparable rates of absorption between the two groups, plasma concentrations of caprylic acid were two- to threefold higher in the cirrhotic patients, immediately after the 60-minute infusion period. This suggested that the capacity of cirrhotic livers to clear absorbed caprylic acid and presumably other MCFAs is compromised (Traul, *et al.*, 2000).

In a subsequent study (Linscheer *et al.*, 1970), in which control and cirrhotic patients were administered a test meal of MCTs (0.5 gms/kg lean body mass), also showed that serum concentrations of caprylic acid were approximately two-fold higher in the cirrhotic group. Furthermore, it was shown that caprylic acid concentrations were four-to fivefold higher in the spinal fluid of cirrhotic patients. MCTs are absorbed and transported directly to the liver, where they are metabolized. In the presence of liver disease such as cirrhosis, the capacity of the liver can be significantly compromised, resulting in decreased clearance of caprylic acid in addition to a decreased production of albumin (Bach and Babayan, 1982). It is not known if this is a causative factor in hepatic encephalopathy. Unesterified caprylic acid is capable of producing CNS toxicity in animal models comparable to that of clinical hepatic encephalopathy, but this was only achieved at serum caprylic acid concentrations 166-800-fold higher than those observed in patients with hepatic encephalopathy. In these studies, the intravenous or intraperitoneal routes of administration of the caprylic acid are unrelated to the likely oral route of exposure in cirrhotic patients. Therefore, it is unlikely that high circulating levels of caprylic acid alone are responsible for the development of hepatic encephalopathy in cirrhosis patients.

It also appears highly unlikely that the consumption of MCTs in the diet would pose any concern for neurological effects as a result of the metabolic release of caprylic acid (Traul, *et al.*, 2000).

## **6. Conclusion**

Due to its unique absorption and metabolism characteristics, MCT oil has been used therapeutically since the 1950s. MCTs have also been used in an increasing number of food and nutrition applications as they offer a number of advantages over long-chain triglycerides, which are metabolized differently and absorbed less quickly. MCTs have been evaluated in acute, subchronic, reproductive, developmental chronic/carcinogenicity and genotoxicity studies in mammals, and in a number of human clinical studies.

The data strongly suggest that MCTs would pose little or no risk from toxicity when consumed as a supplement in a balanced diet at levels up to 15% of the dietary calories or about 50% of the dietary fat.

## **7: Certification**

The undersigned authors of this document- a dossier in support of GRAS status determination for food ingredient use of medium-chain triglycerides – hereby certify that to the best of their knowledge and belief, this document is a complete and balanced representation of available information, favorable as well as unfavorable, known by the authors to be relevant to evaluation of the substance described herein.

(b) (6)

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**SUBMISSION END**