JHeimbach LLC

November 3, 2021

Susan J. Carlson, Ph.D., Director
Office of Food Additive Safety (HFS-200),
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

Dear Dr. Carlson:

Pursuant to 21 CFR Part 170, Subpart E, Nestlé Nutrition, through me as its agent, hereby provides notice of a claim that the addition of medium chain triacylglycerol (MCT) to exempt infant formula intended for consumption by infants born at term, including infants with cow's milk protein allergy, food allergies, and fat malabsorption, is exempt from the premarket approval requirement of the Federal Food, Drug, and Cosmetic Act because Nestlé Nutrition has determined that the intended use is generally recognized as safe (GRAS) based on scientific procedures.

This is a resubmission of a notice sent in February which FDA declined to file due to formatting errors, which have now been corrected.

A CD is enclosed containing Form 3667, the GRAS monograph, and the signatures of members of the GRAS panel in a zip directory produced through COSM.

If you have any questions regarding this notification, please feel free to contact me at 202-320-3063 or jh@jheimbach.com.

[redacted]

. Heimbach, Ph.D., F.A.C.N.
President

Encl.

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Determination of the Generally Recognized as Safe Status of the Addition of Medium Chain Triacylglycerol to Exempt Infant Formulas

Prepared for
Nestlé Nutrition
Arlington, VA

Prepared by
JHeimbach LLC
Port Royal VA

February 2021
(Revised November 2021)

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1. Signed Statements and Certification

1.1. GRAS Notice Submission

Nestlé Nutrition, through its agent JHEIMBACH LLC, hereby notifies the Food and Drug Administration that the use of medium chain triacylglycerol as described below is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because Nestlé has determined through scientific procedures that this use is generally recognized as safe (GRAS).

[redacted]

James T. Heimbach, Ph.D., F.A.C.N.
President, JHEIMBACH LLC

February 23, 2021
Date

1.2. Name and Address of Notifier

Contact:	Cheryl Callen Senior Director, Regulatory Affairs Nestlé Nutrition 1812 North Moore Street Arlington, VA
Telephone:	571-457-5670
E-mail:	Cheryl.callen@us.nestle.com
Agent:	James T. Heimbach, Ph.D., F.A.C.N. President JHeimbach LLC 923 Water Street #66 Port Royal VA 22535
Telephone:	804-742-5543
E-mail:	jh@jheimbach.com

1.3. Name of Notified Substance

The ingredient that is the subject of this GRAS determination is medium chain triacylglycerol (MCT). The primary fatty acids in medium-chain triacylglycerol are octanoic acid (C8:0), also known as caprylic acid, and decanoic acid (C10:0), also known as capric acid. In this document, the two fatty acids are referred to as octanoic and decanoic except in direct quotations. Although they occur less frequently, for consistency the terms hexanoic (C6:0), dodecanoic (C12:0), and tetradecanoic (C14:0) acids are used rather than the trivial names caproic, lauric, and myristic acids, respectively.

1.4. Intended Use and Consumer Exposure

MCT is intended to be added to exempt infant formulas intended for infants born at term, including those formulas for infants with cow's milk protein allergy, food allergies, and fat malabsorption. The concentrations of MCT in formula vary but can be up to 50% of the fat in exempt infant formulas. An infant formula with a total fat level between 5 and 6 g/100 kcal and 50% of the fat as MCT would range in MCT content from 2.5 to 3.0 g MCT/100 kcal. This is equivalent to 17.0 to 20.3 g MCT/L in formula as consumed.

1.5. Statutory Basis for GRAS Determination

Nestlé's GRAS determination for the intended use of MCT is based on scientific procedures as described under 21 CFR §170.30(b). A comprehensive search of the literature through August 2020 was conducted by JHeimbach LLC; the information was critically evaluated and summarized in a GRAS monograph providing information supporting the GRAS status of MCT for addition to a wide variety of adult and pediatric enteral formulas intended for feeding of individuals with fat malabsorption issues or fatty acid oxidation disorders, needing non-protein energy supplementation, or requiring a ketogenic diet. This latter category included those suffering from Alzheimer's disease and both child and adult epilepsy patients, especially those subject to frequent seizures. The literature review was then extended through December 2020. The complete literature review summarizes the totality of the generally available information germane to determining the safety of the intended use of MCT in infant formula described in this monograph.

Metabolic studies indicate that the smaller molecular weight of medium chain fatty acids (MCFA) allows them to be absorbed more easily and more quickly than are long chain fatty acids (LCFA) as they follow the portal venous system rather than the lymphatic system. They are rapidly oxidized, and little, if any, is stored in adipose tissues. Numerous toxicity studies reported little evidence of toxicity in experimental animals, and the extensive research in which MCT has been consumed by human infants, children, and adults—including healthy and severely compromised individuals—demonstrates the safety of MCT. Although MCT is ketogenic and may cause ketoacidosis or ketonemia at high intakes, these have not been reported at typical or intended levels of consumption. No other potentially adverse effects of MCT have been reported.

MCT is safe under the intended conditions of use because the intake of MCT resulting from these uses is within levels shown by animal and human studies of MCT and other triacylglycerols to be tolerable and safe in the judgment of a panel of experts qualified by scientific training and experience to evaluate the safety of substances added to food, who also determined the intended use of MCT to be GRAS based on publicly available and accepted information (scientific procedures).

Determination of the safety and GRAS status of the intended use of MCT was made through the deliberations of a panel of experts (GRAS Panel) consisting of Joseph F. Borzelleca, Ph.D., James T. Heimbach, Ph.D., and Robert J. Nicolosi, Ph.D., who reviewed information in this monograph and other information they deemed appropriate. The GRAS Panel critically reviewed the publicly available information, including the potential intake of MCT, and

unanimously concluded that the generally available information on MCT contains no evidence that demonstrates or suggests reasonable grounds to suspect a hazard to the public health under its intended conditions of use.

It is the unanimous opinion of the GRAS Panel that other qualified scientists reviewing the same publicly available information would reach a similar conclusion. Therefore, the intended use of MCT in exempt infant formulas is GRAS by scientific procedures.

1.6. Premarket Exempt Status

The intended use of medium chain triacylglycerol is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because Nestlé has determined through scientific procedures that this use is generally recognized as safe (GRAS).

1.7. Availability of Information

The data and information that serve as the basis for this GRAS determination will be sent to the FDA upon request or are available for the FDA's review and copying at reasonable times at the office of James T. Heimbach, Ph.D., President, JHEIMBACH LLC, 923 Water Street #66, Port Royal VA 22535, telephone 804-742-5543 and e-mail jh@jheimbach.com.

1.8. Freedom of Information Act Statement

None of the information in this GRAS notice is exempt from disclosure under the Freedom of Information Act, USC 552.

1.9. Certification

To the best of my knowledge, this GRAS notice is a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to me and pertinent to the evaluation of the safety and GRAS status of the intended use of medium chain triacylglycerol.

1.10. FSIS Statement

Not applicable.

1.11. Name, Position, and Signature of Notifier

James T. Heimbach, Ph.D., F.A.C.N.
President
JHeimbach LLC
Agent to Nestlé Nutrition

2. Identity of the Substance, Method of Manufacture, Specifications, and Physical or Technical Effect

2.1. Chemical Name

The ingredient that is the subject of this GRAS determination is medium chain triacylglycerol or medium chain triglycerides (MCT). The primary medium chain fatty acids (MCFA) in MCT are octanoic (C8:0), also known as caprylic acid, and decanoic (C10:0), also known as capric acid. In this document, the two fatty acids are invariably referred to as octanoic and decanoic except in direct quotations. Although they occur less frequently, for consistency the terms hexanoic (C6:0), dodecanoic (C12:0), and tetradecanoic (C14:0) acids are used rather than the trivial names caproic, lauric, and myristic acids, respectively.

2.2. Trade or Common Names

MCT are also known as caprylic/capric triglyceride and mixed decanoyl and octanoyl triglycerides; when derived from coconut oil, they may be referred to as fractionated coconut oil. MCT are also sold under a variety of trade names.

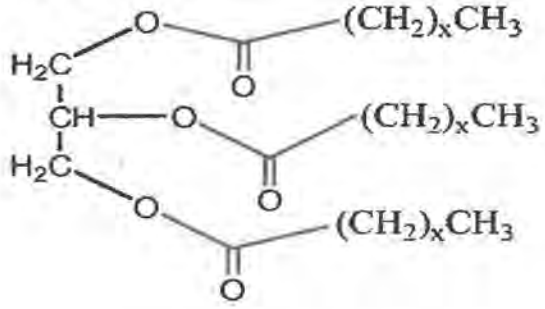
2.3. CAS Registry Numbers

The CAS registry number for MCT is 438544-49-1. The specific MCT product comprising only octanoic and decanoic acids is also listed as 73398-61-5. The CAS registry number for octanoic acid is 124-07-2 and that for decanoic acid is 334-48-5.

2.4. Molecular and Structural Formulas

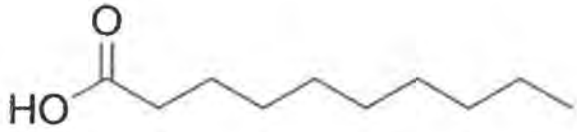
MCT are triacylglycerols in which the fatty acids have aliphatic tails of 6-12 carbon atoms. The MCT that are the subject of this GRAS determination have at least 90% of the fatty acids as octanoic or decanoic acids—i.e., saturated fatty acids with 8 or 10 carbon atoms. The fatty acids are randomly distributed on the glycerol backbone.

The structural formula of MCT is:



Octanoic acid has the molecular formula $C_8H_{16}O_2$ and the structural formula:

Decanoic acid has the molecular formula $C_{10}H_{20}O_2$ and the structural formula:



2.5. Production Process

All substances used in the production are food grade, and all processing is performed under current Good Manufacturing Practice (cGMP).

2.5.1. Starting Materials

MCT are obtained by esterifying glycerol of food-grade vegetable origin with a mixture of octanoic (caprylic) and decanoic (capric) acids that are fractionated from food-grade seed or vegetable oils, most commonly coconut and/or palm kernel oils. (MCFA are found in greatest concentrations in coconut oil, approximately 14% by weight, and also in palm kernel oil [~7.2%] and other oils [USDA 2015].) No chemical catalysts are used during esterification.

2.5.2. Processing Method

The reactor is charged with food-grade glycerol and the appropriate amounts of octanoic and decanoic acids depending on the specific MCT being produced. The esterification reaction takes place at an elevated temperature under nitrogen, with activated carbon to adsorb contaminants. Following the esterification reaction, vacuum is used to remove free (unesterified) fatty acids and the MCT is dried under vacuum, cooled, and filtered. Any volatile compounds formed are removed under reduced pressure by deodorization. The process is illustrated schematically below:

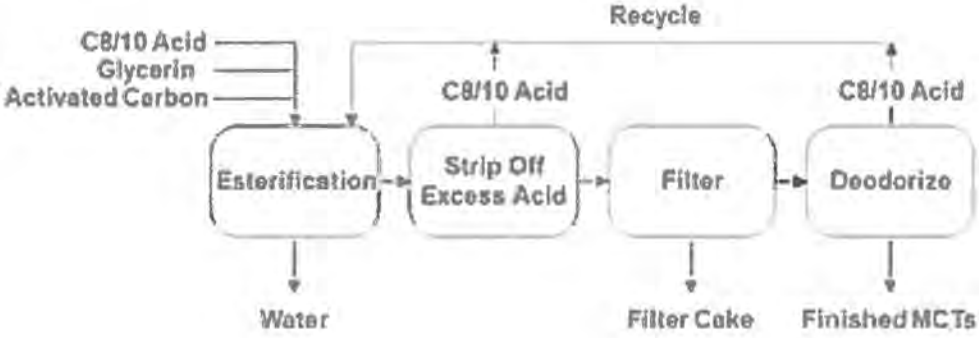


Figure 1. Production Process for Medium Chain Triacylglycerol.

2.6. Food-Grade Specifications

Nestlé has established specifications to assure that MCT used in Nestlé products are food grade. Analyses of 3 nonconsecutive lots of product show that the production process is in control and consistently results in food-grade product meeting all specifications.

Table 1. Specifications for Medium Chain Triacylglycerol.

Parameter	Unit	Specification	Batch/Lot Number		
			0002238522	0002233943	0002226170
Sensory					
Appearance		Oily liquid			
Color		Pale to light yellow	Clear	Clear	Clear
Odor		Bland	Neutral	Neutral	Neutral
Taste		Neutral, bland	Neutral	Neutral	Neutral
Physical Chemical					
Moisture	g/100 g	≤ 0.1	0.03	0.01	0.03
Acid value	mg KOH/g	≤ 0.1	0	0.02	0
Free fatty acids as lauric acid	g/100 g	≤ 0.05	0	0.01	0
Peroxide value ex works	meq. O_2/kg	≤ 0.5	<0.1	<0.1	<0.1
Hexanoic acid C6:0	g/100 g	≤ 1.8	0.1	<0.1	<0.1
Octanoic acid C8:0	g/100 g	40 - 60	57.8	58.3	57.0
Decanoic acid C10:0	g/100 g	20 - 50	32.7	35.6	33.5
Lauric acid C12:0	g/100 g	≤ 1.5	0.2	<0.1	0.2
Iodine value	cg/g	≤ 0.5	0.0	0.0	0.0
Contaminants					
3-MCPD bound in esters	mg/kg	≤ 0.35	0.17	0.26	0.29
Glycidol bound in esters	mg/kg	≤ 0.30	<0.1	<0.1	<0.1
Sum of dioxins and furans (WHO-PCDD/F-TEQ)	pg/g	≤ 0.75	Max 0.3	Max 0.3	Max 0.3
Sum of dioxins, furans and dioxin-like PCBs (WHO-PCDD/F-PCB-TEQ)	pg/g	≤ 1.25	Max 0.5	Max 0.5	Max 0.5
Sum of polychlorinated biphenyls (PCBs) 28, 52, 101, 138, 153 and 180	ng/g	≤ 0.75	Max 1.0	Max 1.0	Max 1.0
Benzo(a)pyrene	µg/g	≤ 2.0	Max 1.0	Max 1.0	Max 1.0
Sum of benzo(a)pyrene, benz(a)anthracene, benzo(b)fluoranthene and chrysene (PAH 4)	µg/g	≤ 3.0	Max 2.0	Max 2.0	Max 2.0
Heavy Metals					
Arsenic	mg/kg	≤ 0.1	Max 0.1	Max 0.1	Max 0.1
Cadmium	mg/kg	≤ 0.02	Max 0.005	Max 0.005	Max 0.005
Lead	mg/kg	≤ 0.1	Max 0.01	Max 0.01	Max 0.01
Mercury	mg/kg	≤ 0.05	Max 0.01	Max 0.01	Max 0.01

Parameter	Units	Specification	Lot Number		
			0002238522	0002233943	0002226170
Contaminant microorganisms					
Aerobic mesophilic organisms		≤ 1,000/g	NA	NA	NA
Coagulase positive *staphylococci*		≤ 10/g	NA	NA	NA
Cronobacter species		Absent/10 g	Absent/10 g	Absent/10 g	Absent/10 g
Enterobacteriaceae		≤ 10/g	Absent/10 g	Absent/10 g	Absent/10 g
Salmonella		Absent/25 g	Absent/25g	Absent/25g	Absent/25g

2.7. Intended Technical Effect

MCT in exempt infant formulas is intended to be a source of dietary fat and energy

3. INTENDED USE AND DIETARY EXPOSURE

3.1. Food Categories and Addition Level of Medium Chain Triacylglycerol

MCT is intended for use in powdered milk-based exempt infant formulas intended for infants with fat malabsorption issues. The addition level is from 17.0-20.3 g MCT/L formula as prepared. Intended uses include only products that are submitted to a heat treatment sufficient to inactivate pathogens.

3.2. Estimated Daily Intake of Medium Chain Triacylglycerol

Typical dose volumes are 700 ml/day for infant formulas with MCT concentrations of 17.0 to 20.3 g MCT/L. Intakes of MCT per 700 ml are 11.9 to 14.2 g per day. For a 4-kg infant, the MCT intake from formula is 3.0 to 3.6 g/kg bw/day.

The powdered milk-based exempt term infant formula will contain between 17.0 and 20.3 g MCT/L as consumed. According to tables of daily energy intake by formula-fed infants provided by Fomon and Bell (1993), the subpopulation of infants with the highest intake per kg body weight is boys aged 14–27 days. The mean energy intake by this group is 121.1 kcal/kg bw/day and the 90th percentile is 141.3 kcal/kg bw/day. Among girls, the highest energy intake is found in the same age group, 14–27 days, and is nearly as high as boys: the mean and 90th energy intake percentiles are 117.8 and 138.9 kcal/kg bw/day. Assuming that the formula is the sole source of nutrition with a caloric density of 670 kcal/L when ready to consume, the formula consumption required to obtain the 90^{th} percentile energy intake is 211 ml/kg bw/day for boys and 207 ml/kg bw/day for girls. These amounts of formula provide 90^{th}-percentile intakes of 3.6-4.3 g MCT/kg bw/day for boys and 3.5-4.2 g MCT/kg bw/day for girls.

4. SELF-LIMITING LEVELS OF USE

There is no reasonable self-limitation to the level of MCT that can be added to infant formula—i.e., a level which is technologically unfeasible. There is of course a nutritional limit to the fat content of infant formula as well as a limit to the content of short-chain fatty acids in order to ensure an adequate amount of essential long-chain fatty acids within the total fat.

5. Experience Based on Common Use in Food Before 1958

The conclusion that the intended use of MCT is GRAS is based on scientific procedures rather than experience based on common use in food prior to 1958.

6. NARRATIVE

6.1. Intake of MCT from Naturally Occurring Sources

Glycerol is found in all lipids in the human food supply, where it forms the backbone of all triacylglycerols. MCFA are found in most naturally occurring lipids, and are present in the greatest concentrations in coconut oil, approximately 14% by weight, and palm kernel oil (~7.2%) according to Release 26 of the *USDA National Nutrient Database for Standard Reference* (USDA 2015). Based on national consumption survey data, the U.S. average consumption of MCFA is ~2% of total fat intake (USDA 2007). Since the mean daily fat intake of individuals in the U.S. is estimated at 74.4 g (USDA 1997), the estimated mean daily intake of MCFA is 1.5 g. It is widely accepted (see FDA 2006) that the 90th percentile dietary intake of a substance can be estimated by doubling the mean, and so the estimated 90th percentile daily intake of MCFA is approximately 3.0 g. The fatty acids constitute approximately 63% of the weight of MCT (depending on the relative proportions of octanoic and decanoic acid), and so an intake of 3.0 g of MCFA indicates an intake of about 4.8 g of MCT.

MCFA are also found in human milk. In a comparison of the milkfat content of breast milk from vegetarians and non-vegetarians in California, Finley et al. (1985) found mean contents of octanoic and decanoic acids combined of 1.30% of total fatty acids in the former and 1.18% of total fatty acids in the latter. Yuhas et al. (2006) analyzed samples of human milk from women in 9 countries and consistently found higher levels of MCFA than those reported by Finley et al. (1985). It is likely that the older estimates were based on extraction methods that recovered only a portion of the MCFA; Greenberger and Skillman (1969) reported that "standard" extraction methods obtained only 40-60% of MCFA. In the later analyses by Yuhas et al. (2006), octanoic and decanoic acids together constituted from 1.65% of the fatty acids (from 46 women in Mexico) to 2.63% (from 54 women in the Philippines); samples from 49 women in the United States had a mean of 1.66% of the fatty acids as octanoic and decanoic acids.

6.2. Absorption and Distribution

Bach and Babayan (1982) reported that the smaller molecular weight of MCT compared to LCT facilitates the action of pancreatic lipase, leading to faster and more complete hydrolysis. Similarly, the smaller molecular weight of MCFA allows them to be absorbed more easily and more quickly than are LCFA. As noted by Greenberger and Skillman (1969), "the interfacial tension between water and medium-chain fatty acids is low, resulting in greater water solubility than that of long-chain fatty acids." In the presence of pancreatic lipase or bile salt deficiency, MCT can still be absorbed whereas LCT cannot. MCFA follow the portal venous system rather than the lymphatic system (Babayan 1987; Greenberger and Skillman 1969), and a minor fraction bypass the liver and are distributed to peripheral tissues via the general circulation (Babayan 1988; Bach and Babayan 1982; Greenberger and Skillman 1969). Very little of the MCT, if any, is stored in adipose tissues (Greenberger and Skillman 1969), nor is it stored elsewhere, but instead the MCFA "are degraded to 2-carbon fragments and ketones or are completely oxidized."

6.3. Metabolism

It has been established that consumption of MCT can lead to ketone production (Bach et al. 1977), but ketone production from consumption of MCT is dose-dependent and neither ketoacidosis or ketonemia have been reported at normal consumption levels of MCT (Freund and Weinster 1966; Bach et al. 1977; Bach and Babayan 1982; Traul et al. 2000).

Three groups of male Sprague-Dawley rats (n = 12 rats/group) weighing 190-250 g (age not reported) were fasted overnight prior to receiving tail-vein injections of ^{14}C-labeled trioctanoate (MCT), ^{14}C-labeled trilinoleate (LCT), or a 75:25 blend of ^{14}C-labeled trioctanoate and unlabeled trilinoleate (Johnson et al. 1990). Rats were maintained in metabolic cages to monitor the radioactivity of exhaled CO_2; blood was taken from 4 rats/group at 0.5, 1, 2, 4, 8, and 24 hours after injection; and 2 rats from each group were sacrificed at 0.5, 1, 2, 4, 8, and 24 hours and liver, kidney, lung, duodenum, spleen, heart, brain, renal fat, epididymal fat pads, brown fat, and muscle were excised for measurement of radioactivity, along with urine and feces.

Approximately 90% of the MCT, compared with only 45% of the LCT, was converted to CO_2 within 24 hours. The half-life of MCT radioactivity in the blood was significantly less than that of LCT, and the amount of radioactivity measured in tissue samples was significantly lower in rats receiving MCT than in those injected with LCT. Johnson et al. (1990) concluded that "MCT is utilized and distributed faster and more completely than is LCT and is not stored within the body."

6.4. Toxicity

These studies are discussed below and summarized in Table 2.

6.4.1. Acute Oral Toxicity

Fasted male Wistar rats (number, age, weight not reported) received single doses ranging from 4.5 to 36.0 ml/kg bw of MCT containing 50-65% octanoic acid and 30-45% decanoic acid. No toxic effects were reported during the 10-day observation period or at necropsy, but animals receiving 18.0 and 36.0 ml/kg consumed less feed and excreted softer feces for the first 2 days. (Klimmer [1971], reported by Traul et al. [2000]).

Traul et al. (2000) reviewed 4 additional unpublished studies of acute oral toxicity (Anonymous 1977; Lewis and Palanker 1977; Palanker 1976a; Palanker 1976b), in each of which 10 Wistar rats (5 rats/sex) were gavaged with 5.0 g/kg bw of a commercial MCT preparation containing 50-65% octanoic acid and 30-45% decanoic acid and observed for 14 days. No adverse observations, abnormal gross pathology findings at necropsy, or deaths were reported at the tested dose.

Tyler's Original strain mice were gavaged with 5.0, 10.0, 20.0 or 25.0 ml/kg bw of a commercial MCT preparation containing 50-65% octanoic acid and 30-45% decanoic acid; no clinical signs or deaths were reported. In a second study with 25.0 ml MCT/kg bw administered by gavage, lethargy and ataxia occurred within 10 minutes after administration and dyspnea was noted in some animals within 1 hour. All animals were reported to be asymptomatic at the end of

the first day, but no necropsy observations were reported. (Poole [1977], reported by Traul et al. [2000]).

Tyler's Original strain mice were gavaged with 12.5, 20.0 or 25.0 ml/kg bw of another commercial MCT product with a slightly higher portion of octanoic acid than that tested in the first two studies. Transient ataxia, lethargy, dyspnea and diuresis were reported 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 group. Two animals that received 20.0 ml/kg bw and one animal that received 25.0 ml/kg bw died. All symptoms disappeared in the survivors by the end of day 3, but no necropsy observations were reported. (Poole [1977], reported by Traul et al. [2000]).

Elder (1980) reported the acute oral toxicity in female mice and male rats (numbers, strains, ages, and bodyweights not reported) of several varieties of MCT with varying proportions of octanoic and decanoic acids. In the first mouse study, lethargy and ataxia were reported within 10 minutes of administration of a dose of 25 ml/kg bw, and dyspnea within one hour. However, all animals appeared asymptomatic 24 hours after administration and there was no mortality. In the second mouse study with doses of MCT ranging from 12.5 to 25.0 ml/kg bw, ataxia, lethargy and dyspnea were reported within 15 minutes, progressing in some animals to full loss of activity by 1 hour. At doses of 20.0 and 25.0 ml/kg bw, 3 of 15 animals died within 48 hours, while surviving animals were reported to be asymptomatic by 72 hours. The authors calculated that the oral LD50 for female mice was greater than 25.0 ml/kg bw. In the first rat study, MCT doses of 18.0 and 36.0 ml/kg bw to male rats did not result in any mortality and no significant findings were reported at necropsy; the oral LD50 for male rats was determined to be greater than 36.0 ml/kg bw.

In a study of food flavorings, the acute oral toxicity of free octanoic acid was assessed in 10 young adult Osborne-Mendel rats (age and bodyweight not reported), 5 of each sex. Animals were fasted for 18 hours prior to administration of octanoic acid by gavage (doses not reported); animals were observed for 2 weeks, during which they had free access to feed and water. Signs of depression and diarrhea were reported, and the calculated oral LD50 for octanoic acid was 10,080 mg/kg bw. (Jenner et al. 1964).

6.4.2. Repeated-Dose Oral Toxicity

Kaunitz et al. (1958) fractionated coconut oil and reconstituted triacylglycerol from saturated fatty acids of 6-12 carbons to create MCT; the distribution of individual fatty acids was not reported. Forty-six 5-week-old male Sherman albino rats (starting bodyweights not reported) were singly housed and fed *ad libitum* diets containing 20% (w/w) of either lard or MCT in addition to 0.09% linoleic acid for 10 to 12 months. (Sixteen rats [8 rats/group] were fed for 10 months, 14 rats [7 rats/group] were fed for 11 months, and 16 rats [8 rats/group] were fed for 12 months.) The daily MCT dose was approximately 15 g/kg bw/day. No overt toxicity was reported and there was no difference in survival between the two groups (17 of 23 rats receiving lard and 19 of 23 rats receiving MCT survived to scheduled termination). Rats fed diets containing MCT gained about 15% less weight during the study than did those receiving lard. This difference was shown not to be the result of fecal fat losses; rats absorbed 98.5% of the

MCT and 97.7% of the lard in their diets. Rats fed the MCT diet had total cholesterol levels significantly lower than rats on the lard diet. The authors concluded that, "Among male rats maintained on diets containing 20% lard or 20% MCT and .09% linoleic acid for 18 months, no differences were observed between the groups other than the depressed body weight and lowered serum cholesterol levels of the group fed MCT."

The chronic toxicity profile of MCT was evaluated in a long-term growth study with 6 groups of Wistar rats, 15 of each sex/group (Harkins and Sarett 1968). The rats (age and weight not reported) were individually housed and fed *ad libitum* diets with 40% of calories from fat for 47 weeks; the fats in the diets given to the 6 groups were MCT (comprising approximately 75% octanoic acid and 25% decanoic acid), oleo oil, butter fat, coconut oil, corn oil, or safflower oil. Daily records were kept of feed consumption; feces were collected periodically for measurement of fat, nitrogen, and calcium; and blood was drawn periodically for analysis of total cholesterol TC). After the rats were euthanized, liver, kidneys, spleen, heart, adrenals, femurs, testes, and epididymal fat pads were excised and weighed; liver and carcass were analyzed for fat; and liver and intestine were examined histologically.

The intake of MCT was approximately 9 g/kg bw/day. At the end of 47 weeks, the mean weight gain for rats fed the MCT diet was not significantly different from those recorded for the other diets with the exception of the coconut oil-based diet, which resulted in significantly greater weight gain. The groups did not differ in mortality over the 47 weeks; 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 differences. Although the type of oil added to the feed influenced the fatty acid composition of epididymal and carcass fat, little octanoic or decanoic acid was incorporated into tissue fat, indicating, according to the study authors, that these fatty acids "are rapidly metabolized to smaller units." Male rats consuming MCT had significantly lower blood TC levels than those consuming the other fats, but female rats exhibited no difference; rats of both sexes had significantly lower concentrations of liver lipids when receiving MCT than when consuming diets with the other fats. The type of fat consumed had no significant effect on absorption of fat, protein, or calcium, nor on the histology of the liver or intestine. The results showed that the MCT diet supported normal growth with no reported adverse effects.

Groups of 10 weanling male Wistar rats (age and weight not available) were gavaged with either 1 or 3 ml/day of a commercial MCT preparation containing 50-65% octanoic acid and 30-45% decanoic acid for 30 days. The volume of the gavage remained constant as the rats grew, and thus the low dose decreased over the course of the study from 7.56 to 3.58 ml/kg bw/day while the high dose declined from 21.3 to 10.8 ml/kg bw/day. No toxic effects or adverse effects on weight gain or urinalysis values were reported, 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], reported by Traul et al. [2000]).

Groups of 20 male and 20 female rats (strain, age, and weight not available) were fed a commercial MCT preparation containing 50-65% octanoic acid and 30-45% decanoic acid at 0, 10,000 or 50,000 ppm in 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 aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and both esterified and non-esterified fatty acids, which were all within the normal range. At necropsy, the absolute and brain-weight-relative weights of the liver, kidney, adrenal gland, thyroid gland, gonads, and brain of the rats fed the MCT were not different from controls. Traul et al. (2000) concluded that this study showed that feeding MCT did not increase triglyceride levels or induce a hyperlipidemic condition and reported that the NOAEL for MCT in the diet in this study was 50,000 ppm (5% dietary concentration), approximately equivalent to 3750 mg/kg bw/day. (Klimmer [1971], reported by Traul et al. [2000]).

Twelve 7-day-old Single Comb White Leghorn male chicks were fed a diet containing a 16% admixture of a commercial MCT preparation containing 50-65% octanoic acid and 30-45% decanoic acid for 3 weeks while a matched control group received standard diet. The chicks consuming the MCT diet had significantly reduced body weight gain and reduced muscle weight. These effects were reportedly due to the reduced feed consumption by chicks receiving the high fat diet, and all mortality was attributed to starvation and not the consumption of MCT. Slight subcutaneous edema was observed in 3 treated birds, but heart fluid volume was minimal in all chicks from treated and control birds and there was no evidence of edema. The absence of "chick edema factor" was determined by the reported absence of hydropericardium, hydroperitoneum, or subcutaneous edema at necropsy. The necropsy did not reveal any abnormal changes in liver or kidney. The authors concluded that the results of this study showed that "MCT does not contain chick edema factor" and that "MCT is not toxic to chicks." The 16% dietary concentration is approximately equivalent to a dose of 20 g/kg bw/day. (Roth and Shapiro [1981], reported by Traul et al. [2000]).

As part of a larger study assessing the absorption and nutritive value of docosanoic (behenic—C22:0) acid, Webb et al. (1991) investigated the subacute oral toxicity of caprenin, a mixed-chain MCT/LCT consisting of octanoic (23.2%), decanoic (26.6%) and docosanoic (45%) acids, in male and female weanling Crl:CD BR Sprague-Dawley rats. Sixty rats of each sex, aged 4 weeks and weighing 88-107 g (M) and 83-96 g (F), were randomly assigned to 4 groups, each containing 15 rats of each sex. Rats were individually housed and given free access to water and a diet containing 0, 5, 10, or 15% caprenin, plus enough corn oil to maintain total fat content at 18% and maintained on these diets for 28 days. Animals were observed twice daily for mortality, moribundity, and indications of toxic effects; feed intake and bodyweights were measured weekly and the rats were given physical examinations each week. Ophthalmoscopic examinations were performed at initiation and at week 4.

At the end of the 28 days, 10 rats/sex/group were fasted overnight and blood was taken through the orbital sinus for clinical chemistries (sodium, potassium, chloride, calcium, inorganic phosphorus, glucose, total bilirubin, blood urea nitrogen [BUN], total protein, albumin, globulin, creatinine, TC, lipoproteins, triacylglycerol [TAG], γ-glutamyl transferase [GGT], alkaline phosphatase [ALP], AST, and ALT) and hematology (total and differential leucocyte counts, erythrocyte count, hemoglobin, hematocrit, platelet count, cell morphology, reticulocyte count, mean cell volume [MCV], mean cell hemoglobin [MCH], and mean cell hemoglobin

concentration [MCHC]). Blood was also taken from the abdominal aorta for coagulation measures (prothrombin time and activated partial thromboplastin time). Tissues (brain, spleen, liver, kidneys, heart, gonads, adrenals, cecum, and colon) were excised for weighing and taxonomic assessment. The remaining 5 rats/sex/group were examined for tissue fat content and fatty acid composition.

There was no mortality. Female weight gain was similar across all groups, but male rats had dose-dependently lower weights when consuming diets containing caprenin—while male control rats weighed 324.6±24.1 g at study termination, rats consuming the high-dose caprenin diet weighed only 286.5±18.0 g. (The authors noted that, because caprenin provides only about 5 kcal/g while corn oil provides 9 kcal/g, the diets were not isocaloric.) Both males and females in the high-dose caprenin group consumed significantly more feed than did control rats. Absolute liver weights of caprenin-group male rats were significantly lower than those of controls, but relative weights did not differ significantly. Absolute cecum weights were significantly reduced in low- and mid-dose male rats, but not in high-dose males or in females. Kidneys and testes of males in all treatment groups showed significant increases in relative weights, but no differences in absolute weights. Female rats in the high-dose group had significantly increased absolute and relative kidney weights.

ALT values were significantly increased at all dose levels in females and in the high-dose males; differences in other clinical chemistry parameters were inconsistent, failed to show a dose-related trend, and were within historical reference values. The only significant differences in hematology were elevated platelet counts in high-dose males and hemoglobin levels in mid-dose females. No gross pathological lesions were reported; "a relatively few microscopic alterations were noted but were considered unrelated to treatment." Diet had no effect on the fat content of the heart, but rats consuming caprenin rather than corn oil had significant dose-related reductions in the fat content of the liver.

Webb et al. (1991) noted that ALT values are positively correlated with dietary protein intake, and thus the increased ALT levels reported in rats consuming diets containing the lower-calorie caprenin rather than corn oil are expected since these diets provided relatively more protein. After discussion of the other inconsistent changes reported, the authors concluded that "An important outcome of the 28-day feeding study with rats was the absence of any toxicity for levels of [caprenin] ranging up to 15% of the diet (83% of total dietary fat." The authors did not report a NOAEL; however, since the highest dietary concentration tested, 15%, equivalent to 14.5 g/kg bw/day in males and 16.4 g/kg bw/day in females, did not elicit any adverse effects, it is the NOAEL.

Groups of 25 male and 25 female weanling Crl:CD BR Sprague-Dawley rats aged 4 weeks and weighing 71-98 g (M) and 68-88 g (F) were fed caprenin at 0, 5.23, 10.23 or 15.00% in the diet for 91 days (Webb et al. 1993). Caprenin is a mixed-chain MCT/LCT consisting of octanoic (23.2%), decanoic (26.6%) and docosanoic (behenic—C22:0, 45%) acids. Control animals were fed diets containing 12.1% corn oil or 11.2% MCT oil (not further defined). All diets contained at least 3% corn oil to provide essential fatty acids; all diets provided about 4000 kcal/kg bw and provided 26.8% of dietary calories as fat. Animals were individually housed and

had free access to feed and water; they were observed twice daily for mortality, moribundity, and any indication of toxic effects. Feed intake and bodyweights were measured weekly and the rats were given physical examinations. Ophthalmoscopic examinations were performed at initiation and at week 13.

On day 91, 20 rats/sex/group were fasted overnight and blood was taken through the orbital sinus for clinical chemistries (sodium, potassium, chloride, calcium, inorganic phosphorus, glucose, total bilirubin, BUN, total protein, albumin, globulin, creatinine, TC, lipoproteins, TAG, GGT, ALP, AST, and ALT) and hematology (total and differential leucocyte counts, erythrocyte count, hemoglobin, hematocrit, platelet count, cell morphology, reticulocyte count, MCV, MCH, and MCHC). Blood was also taken from the abdominal aorta for coagulation measures (prothrombin time and activated partial thromboplastin time). Tissues (brain, spleen, liver, kidneys, heart, gonads, adrenals, cecum, and colon) were excised for weighing and taxonomic assessment. The remaining 5 rats/sex/group were examined for tissue fat content and fatty acid composition.

There were no treatment-associated deaths and clinical observations revealed no findings that were uncommon or at increased frequency for animals of this type and age, with the exception of increased incidences of tail desquamation in animals receiving 11.2% MCT oil. There were no significant differences in body weights or body weight gains across all groups. In the groups fed caprenin, females had significantly lower absolute liver weights while male rats exhibited lower relative liver weights; both of these observations—which did not exhibit dose-dependence—were attributed to reduced deposition of fat in the livers. Males on the 15.00% caprenin diet consumed significantly more feed and females consumed significantly less feed than either the corn oil or MCT dietary groups. Differences in clinical chemistry and hematologic values across all groups were considered by the authors to be not toxicologically significant "since they fell within the normal historical range for rats of this sex and strain." The necropsy findings included granular renal changes for females receiving the highest dose of caprenin; this finding may be related to nephrocalcinosis that occurs normally in female rats. No other gross or histopathological findings were reported. There were no significant differences among groups in the fat content of the hearts, livers, or perirenal fat pads. The NOAEL for caprenin was the highest tested dietary concentration of 15%, equivalent to 13.2 and 14.6 g/kg bw/day for males and females, respectively. For MCT, the NOAEL was the single dietary concentration tested, 11.2% of the diet, equivalent to approximately 9.2 g/kg bw/day (Webb et al. 1993).

The US National Toxicology Program (NTP 1994) evaluated the long-term (2 years) toxicity and potential carcinogenicity of tricaprylin (trioctanoin), a synthetic triacylglycerol (CAS No. 538-23-8) in which all three fatty acids are octanoic acid. In this study, which was conducted in compliance with FDA Good Laboratory Practice (GLP) regulations, groups of 60 seven-week-old male F344/N rats were gavaged with 0, 2.5, 5 or 10 ml tricaprylin/kg bw/day 5 days/week for 2 years. The volumes used in the study, 2.5, 5, and 10 ml/kg bw, were regarded by NTP as the minimum, standard, and maximum volumes of oils that could be reasonably administered to rats over a 2-year period. The rats were housed 5/cage and had free access to feed and water. Animals were observed twice daily and weighed weekly for 14 weeks and

monthly thereafter. At 15 months, 10 rats from each dose group were randomly selected for hematology with blood drawn from the posterior vena cava; parameters included hematocrit, hemoglobin, erythrocyte count, MCV, MCH, MCHC, reticulocytes, and total and differential leukocyte counts. At necropsy, organs and tissues were examined for gross lesions and subjected to microscopic histopathologic examination. Tissues examined included adrenal gland, bone and marrow, brain, esophagus, gross lesions, heart, kidney, large intestine (cecum, colon, rectum), liver, lung, mammary gland, lymph nodes (mandibular and mesenteric), pancreas, parathyroid gland, pituitary gland, preputial gland, salivary gland, skin, small intestine (duodenum, jejunum, ileum), spleen, stomach, testis with epididymis and seminal vesicle, thymus, thyroid gland, tissue masses, trachea, and urinary bladder.

The survival of rats receiving 10 ml tricaprylin/kg bw/day was significantly lower than that of the controls. Clinical findings of dyspnea, ataxia, and lethargy following dosing were recorded for 50 of the 60 animals receiving 10 ml tricaprylin/kg bw/day. However, the animals generally recovered prior to the next daily dosing, and the incidence of clinical findings declined during the second half of the study. The 2-year survival of high-dose tricaprylin rats was less than that of the control rats or rats receiving lower doses (0 ml/kg bw/day—31/50; 2.5 ml/kg bw/day—30/50; 5 ml/kg bw/day—31/50; 10 ml/kg bw/day—23/53) due to moribund kills and deaths that appeared to be related to toxicity. Both feed consumption and mean body weight of the high-dose group were significantly lower than that of the controls throughout the study; feed efficiency ratios did not appear to be significantly different.

There were significant dose-related increased incidences of pancreatic exocrine hyperplasia and adenoma (hyperplasia: 8/49, 9/49, 18/49, 28/50; adenoma: 2/49, 6/49, 13/49, 18/50 in the 0, 2.5, 5 and 10 ml/kg bw/day groups, respectively). 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). The incidence of nephropathy was significantly decreased in high-dose rats, and the severity of nephropathy decreased with increasing dose (incidence [mean severity grade]: 46/50 [2.0], 42/50 [1.5], 45/50 [1.7], 27/49 [0.9]). In high-dose group rats, the incidence of mononuclear cell leukemia was significantly decreased (23/50, 28/50, 22/50, 9/53). The NTP (1994) concluded that, "Tricaprylin at 10 ml/kg was toxic, with the animals showing lethargy, ataxia, dyspnea, decreased weight gain, and increased mortality. The toxicity may have been due to the large volume of triglycerides in each dose and is consistent with severe ketosis." The NTP also reported that the oxidation of medium-chain fatty acids reduces fat deposition, and suggested that "This would explain the lower mean body weights in the rats receiving the high volume of tricaprylin."

Although the study report did not identify a NOAEL, since there were no statistically significant differences in any of the observed parameters between the untreated control rats and those receiving 2.5 ml tricaprylin/kg bw/day group, the NOAEL for oral tricaprylin would be 2.5 ml/kg bw/day or about 2.37 g/kg bw/day, the lowest level tested.

Miglyol 812®, a mixture of MCT comprising 57% octanoic, 41.4% decanoic, and 0.6% dodecanoic acid, is widely used as an excipient. To assess its oral toxicity in rats, Sellers et al. (2005) dosed by gavage fifteen 6-8-week-old male and female Wistar Han IGS rats/sex/dose for

8 weeks with 10 ml MCT/kg bw/day MCT or 0.6% dietary concentration of a mixture of methylcellulose and Tween 80 as a control. Starting bodyweights of the rats were not reported[1]; they were individually housed with free access to feed and water. Dosing continued for 4 weeks, followed by a 4-week recovery period. The animals were observed daily, weighed twice weekly, and had feed consumption assessed weekly. Blood was taken at baseline, day 28, and the end of the recovery phase and analyzed for total erythrocyte count, hemoglobin, hematocrit, MCV, MCH, MCHC, total and differential leukocyte count, platelet count, sodium, potassium chloride, phosphorus, calcium, BUN, bilirubin, ALT, AST, ALP, total protein, albumin, globulins, creatinine, glucose, TC, and TAG. Urine samples taken on day 27 and on the final day of recovery were analyzed for sodium, chloride, phosphorus, calcium, and potassium.

Ten rats/sex/group were sacrificed on day 28 and 5 on day 56 and subjected to complete necropsies, including collection of adrenal glands, lung, testes, aorta, lymph node (mesenteric and mandibular), thymus, femur and sternum, thyroid glands, mammary gland, tongue, bone marrow, ovaries, trachea brain, pancreas, urinary bladder, cecum, parathyroid glands, uterus, cervix, pituitary gland, vagina, colon, prostate gland, duodenum, rectum, epididymides, salivary gland, esophagus, sciatic nerve, eyes with optic nerves, seminal vesicles, Hardarian glands, skeletal muscle, heart, skin, ileum, spinal cord, jejunum, spleen, kidneys, stomach, and liver; adrenal glands, brain, heart, kidneys, liver, ovaries, prostate gland, testes, and thyroid glands were weighed.

There was no mortality. MCT consumption resulted in soft and/or mucoid stooling in over 75% of the rats of both sexes, but this effect lasted only 0-8 days in males and 0-5 days in females. Feed intakes of males and females consuming MCT were 66% and 84%, respectively, of that of control animals, and bodyweight gain was significantly reduced in both sexes. Feed-efficiency ratios were not reported, but the reduced weight gain appears to be attributable to reduced feed intake due to intake of MCT. Hematology parameters were not affected by MCT intake, but significant increases from baseline values were reported in serum levels of TAG and TC as compared to controls; serum levels of protein, globulins, and BUN were significantly reduced but remained within the normal historical reference ranges for age-matched Wistar Han rats. Alveolar histiocytosis was significantly more frequently reported in rats gavaged with MCT than in control rats, but this condition is common in older rats and is often seen in gavage studies; the authors attributed it to aspiration of the dosing material. Both absolute and relative weights of thymus were significantly lower in males and females receiving MCT, but were not accompanied by any histological changes in the thymus. All reported effects during dosing were not observed during recovery. While the authors did not report any effects indicating toxicity, suggesting a NOAEL of 10 ml/kg bw/day, the only dose tested, equivalent to 9.5 g/kg bw/day, they concluded that MCT "should not be considered innocuous when delivered by oral gavage in long-term rodent toxicology studies."

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[1] The article included a graph of bodyweights through the 28-day dosing period; the mean starting bodyweights appear to be about 250 g for males and 180 g for females.

Matulka et al. (2009) reported a study in which MCT (not further described) was administered to beagles in the form of dietary admixtures containing 0, 5, 10, and 15% MCT for 90 days. Sixteen dogs of each sex, aged 1-6 years (bodyweights not reported), were individually housed and adapted to a 3-hour-per-day feeding regimen during which they consumed approximately 200 g feed; 4 dogs of each sex were assigned to each feeding group. Clinical observations (lethargy, abrasions, etc.) and measurement of feed and water consumption were done twice daily. Animal bodyweights were measured on the day of receipt, 2 days prior to the study, and at weekly intervals from study day 1. Physical examinations (body temperature, respiration, etc.) were made on Day 1 and during weeks 4, 8, and 12 and ophthalmic examinations were performed at baseline and at the end of the study.

Blood and urine samples were collected 6 days prior to the start of the study and on days 29, 58, and 91. Blood was analyzed for hematology (blood smear morphology, erythrocyte count, hematocrit, hemoglobin, MCV, MCH, MCHC, platelet count, reticulocyte count, total and differential leukocyte counts), clinical chemistries (albumin, ALT, ALP, AST, total calcium, chloride, cholesterol, creatine kinase, creatinine, direct bilirubin, GGT, globulin, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, bilirubin, total protein, TAG, and BUN), and cell pathology. Urine analysis included the appearance, color, bilirubin, ketone levels, occult blood, pH, urine glucose and protein levels, urobilinogen, specific gravity, volume, and a microscopic examination of sediment. All animals were returned to stock at the conclusion of the study, and so there was no necropsy and no tissues or organs were excised.

There was no mortality or significant differences in bodyweights or bodyweight changes among the groups; although some palatability effects were seen early in the study with the MCT-containing diets, there were no overall differences in feed intake. Findings from the physical and ophthalmic examinations were unremarkable and there were no significant differences in hematological indices. With regard to biochemistries, the mid- and high-dose dogs of both sexes showed significant increases in BUN and decreases in urine volume and concomitant increased specific gravity. The authors concluded that, "Based on the findings from this 91-day MCT feeding study, there are no indications of toxicological effects in dogs fed up to 15% MCT in the diet. . . . Therefore, a logical conclusion from this study is that the no-adverse-effects level (NOAEL) for the canine is 15% MCT in feed." Based on the authors' statement that the dogs consumed approximately 200 g feed/day, intake of MCT at 15% dietary concentration was approximately 30 g/day. Assuming mean weights of 10-11 and 9-10 kg for adult male and female beagles, respectively, the NOAEL is equivalent to approximately 3 g MCT/kg bw/day for both sexes.

Le Bars et al. (2015) assessed the oral toxicity of Miglyol 812® (MCT comprising 57% octanoic, 41.4% decanoic, and 0.6% dodecanoic acid) in Göttingen® minipigs, which received the MCT by gavage at doses of 0.5 or 2 ml/kg bw/day with control minipigs receiving a carboxymethylcellulose/Tween 80 mixture in water at 2 ml/kg bw/day for 6 weeks. Three minipigs/sex/group, aged 4 months and weighing 7.1-9.0 kg (males) and 7.1-9.7 kg (females), were individually housed, given free access to water, and given 2 feed rations per day calculated to maintain their starting weight. Animals were observed twice daily and weighed weekly. Ophthalmologic and cardiovascular examinations were performed at baseline and at the end of

dosing and blood was drawn for analysis of hematology (erythrocyte count and associated parameters, total and differential leukocyte count), coagulation (fibrinogen, prothrombin time, and activated partial thromboplastin time), and serum biochemistry (ionogram, hepatic enzymes, lipids, creatinine, glucose, BUN, albumin, and total protein). Urine sampled at the end of dosing was analyzed for urobilinogen, pH, leukocytes, nitrites, proteins, occult blood, ketones, bilirubin, and glucose. After euthanasia, selected organs were removed and weighed and tissues were examined histopathologically. The tissues evaluated were the adrenal glands, brain, bronchus, caecum, colon, duodenum, epididymides, gall bladder, heart, ileum, jejunum, kidneys, liver, lung, esophagus, ovaries, pancreas, spleen, stomach, testes, and thymus.

No deaths occurred in any group. Tremors were reported in 2 of 3 males and 1 of 3 females in the low-dose group and in all 3 males and 1 female in the high-dose group; other clinical signs were sporadic, including dry feces and noisy respiration and dyspnea, but all clinical signs were transient. No significant or toxicologically meaningful effects were reported in feed consumption, bodyweight, ophthalmology, cardiovascular endpoints, hematological or coagulation parameters, or organ weights. Minipigs of both sexes receiving MCT showed a significant increase in serum TAG and a decrease in BUN; males only were reported to have increased serum total and LDL cholesterol. Chronic bronchiolo-alveolar inflammation was reported in 2 of the 3 high-dose males and 1 high-dose female. Although not all animals were affected and there was no dose-effect relationship, these effects were regarded by the authors as related to the administration of MCT at 2 ml/kg bw/day, equivalent to 1.9 g/kg bw/day. The authors concluded that "the oral administration of Miglyol 812® for six consecutive weeks induced some adverse effects in the minipig. . . . the dosing volume and/or concentration of Miglyol 812® for subchronic oral toxicity studies should be limited in the minipig."

While the authors did not report a NOAEL in this study, the absence of reported adverse effects at the low dose or 0.5 ml/kg bw/day would indicate that this was the NOAEL.

The authors conceded that the observed adverse effects were due to gavage dosing and aspiration of a viscous material rather than to toxicity. After observing that "the main findings noted in this study were observed in the lung," they went on to explain:

> "These pulmonary lesions are considered to represent local effects, secondary to the aspiration of the dosing material. It has been demonstrated that oral gavage administration, even with small volumes, can result in passive gavage related-reflux. . . An important risk factor for the occurrence of gavage related-reflux is the viscosity of the test formulation. It has been established that a gavage administration of an oil-based formulation is associated with greater toxicity than a gavage administration of an aqueous-based formulation. . . . The diffuse lesions observed in the lung were considered to be likely related to the aspiration of the viscous dosing material, Miglyol 812®, during the dosing procedure" (Le Bars et al. 2015).

The gavage issues render the toxicological findings unclear, limiting the usefulness of this study in the evaluation of the safety of the test article.

6.4.3. Developmental and Reproductive Toxicity

The developmental and reproductive toxicity of MCT was evaluated in forty-six 5-week-old Sherman albino rats fed diets for 10-12 months containing 20% of lard or MCT comprising saturated fatty acids of 6-12 carbons; the distribution of individual fatty acids was not reported (Kaunitz et al. 1958). Linoleic acid was added at a level of 0.09% to each diet. When treated male rats were mated at 9 months of age with either treated or control females, all males were found to be equally fertile and litters were normal with respect to number and weight. (Surviving male rats were mated again with untreated females at 18 months, and fertility was 87% among males that had received MCT and 69% among those that had received lard.) However, the lactation performance of females receiving the MCT diet was reported to be poor, as shown by lower survival and growth rates of the pups. While the authors offered no explanations for this effect, it may have been due to the relatively low level of available fat to the animals receiving nearly all lipid intake in the form of MCT. The pups from females that had been maintained on the MCT diet were maintained on MCT + 0, 0.09, or 2% linoleic acid. Half of the males on the 0% linoleic supplement died while there were no deaths among males receiving 0.09 or 2% linoleic acid; however, all survivors and all rats of the other groups grew to weights which correlated with the amount of linoleic acid given (mean final bodyweights of 190, 236, and 269 g among males receiving 0, 0.09, or 2% linoleic acid, respectively). While dietary levels of linoleic acid affected offspring growth and survival parameters, the incorporation of 20% MCT (approximately equivalent to 15 g/kg bw/day) did not elicit adverse effects on reproduction.

In a reproductive toxicity study (Harkins and Sarett 1968), young adult male and female McCollum-Wisconsin rats (the F_0 generation; numbers and bodyweights were not reported) were fed a balanced diet containing 40% of calories from fat (21.0% fat by weight), either an MCT comprising 75% octanoic acid and 25% decanoic acid, or oleo oil for 3 weeks before mating. Both diets contained 2.5% safflower oil to supply essential fatty acids. A third group of rats received a low-fat diet with 5% calories from safflower oil. After mating, the rats were singly housed.

The groups did not differ in the number of pups (F_1 generation) per litter or birthweights, but the mean weight of the pups at weaning was significantly higher for dams receiving the high-fat diets (which did not differ) than those on the low-fat diet. There was no difference in mortality during lactation between the MCT and oleo-oil diets. The F_1 rats were raised on the diets fed their dams, and the weights at 49 and 105 days did not differ between the two high-fat groups. At 12 weeks, each group of F_1 rats was randomly divided into 3 subgroups, with each subgroup receiving a different diet (40% of calories from MCT or oleo-oil or 5% of calories from safflower oil). The F_1 females were mated after 3 weeks and the F_2 pups were raised to the age of 63 days.

There were no differences among groups in F_2 generation litter sizes or birthweights, At weaning (21 days), the mean bodyweights were significantly higher among the pups whose dams were receiving a high-fat diet (MCT or oleo oil) than those fed a low-fat diet. In both the F_0 and F_1 generation dams, the diet had no effect on the quantity of milk secretion or on the total fat content. The milk of dams ingesting MCT contained a significantly higher proportion of octanoic and decanoic fatty acids than did the milk of those fed oleo oil (23.3% v. 8.0%), but the

proportion was substantially less than the fraction of octanoic and decanoic acids in the MCT of their diets. The authors suggested that, "It is apparent that the rats fed MCT were required to synthesize a large portion of the fatty acids secreted in the milk fat," but concluded that "the MCT diet also supported normal reproduction, as indicated by litter size and number." Further, the authors reported that, "After weaning, growth of the rats fed MCT compared favorably with that attained by the animals on the diet containing oleo oil." It may be concluded that this study found no indications of adverse effects of a diet containing 40% of the calories as MCT on reproduction or development.

Azain et al. (1993) reported on the effects of feeding MCT to Yorkshire x Landrace or Yorkshire x Duroc sows during late gestation and early lactation on survival of neonatal piglets. Fifty-four sows were randomly assigned to one of 3 feeding groups—MCT (n = 17), LCT (n = 19), or control (n = 18). Beginning on gestation day 91 and continuing through lactation day 7, sows were fed isocaloric and isonitrogenous amounts of feed containing 2% soybean oil and 10% MCT, 10% LCT, or no additional lipid. Sows were induced to farrow on gestation day 112. Litters were weighed at birth and on postnatal days 1, 3, 7 and 21.

There was no effect of treatment on average sow weight at any time and no difference in the number of live piglets at birth. Survival was significantly improved in litters from sows fed MCT relative to litters from sows fed the control diet; overall survival was 90%, 81%, and 80% in the MCT, LCT and control groups, respectively. The greatest improvement in survival was observed in pigs weighing less than 900 g at birth with survival of 68%, 53%, and 32% in the MCT, LCT and control groups, respectively. 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 MCT. The authors concluded that "MCT may provide a practical means to improve survival rates."

The developmental toxicity of an intravenously administered 3:1 mixture of MCT ("composed primarily of 8- and 10-carbon fatty acids and a trace of 6- and 12-carbon fatty acids") and LCT (from soybean oil) to rats and rabbits was reported by Henwood et al. (1997). (The authors explained that intravenous administration was chosen because MCT may be used in either enteral or parenteral nutrition.) The rat study employed mated Crl:CD BR rats weighing 150-200 g on the day of gestation, and the rabbit study used mated Hra:(NZW)SPF rabbits aged 5.5-6.5 months and weighing 3,300-4,446 g at gestation. In both studies, animals were individually caged with free access to feed and water. Animals were randomly assigned to one of 3 groups: low-dose group receiving intravenous administrations of 1 g test article/kg bw/day (25 rats, 15 rabbits), high-dose group receiving 4.28 g/kg bw/day (28 rats, 15 rabbits), or control group receiving saline (24 rats, 15 rabbits). Rats were dosed intravenously via a caudal vein on gestation days 6-15, while rabbits were given intravenous infusions via a marginal ear vein on gestation days 7-19; each infusion lasted 4-5 hours to approximate longer-term administration in humans.

Animals were observed twice daily for mortality, moribundity, and clinical signs. Feed consumption and bodyweight were measured daily. On gestation day 20 (rats) or 29 (rabbits),

animals were euthanized and subjected to internal examination for macroscopic abnormalities; ovaries were removed and examined and the number of corpora lutea recorded; uteri were excised and weighed and the number and placement of implantation sites were recorded. Conceptuses were removed and live fetuses were weighed and examined before being euthanized. Internal organs of rabbit fetuses were examined for variations and malformations of both viscera and skeletons; half of the rats were examined for visceral variations and half for skeletal variations.

Rats and rabbits in the high-dose group had significantly reduced feed consumption, an expected finding since the test article had substantial caloric value. High-dose rats showed a dose-dependent increase in tail lesions due to extravasation of the test article into perivascular areas. There was a "trend toward" an "increasing incidence of necropsy findings" in the high-dose rats, but no single finding was significant. All female rats, with the exception of one control rat, were pregnant and had at least one viable fetus/litter. There were no significant differences in pre- or post-implantation loss, in the percentage of live or resorbed fetuses, or in their mean bodyweights; there were no dead fetuses in any group. There were no test-article-related fetal external, visceral, or skeletal observations in rats.

In the rabbit study, there were no test-article-related maternal effects reported at necropsy, and all pregnant animals had at least one viable fetus. However, the high-dose rabbits had a significantly higher proportion of resorptions/litter than the controls, and mean fetal bodyweights were significantly lower. The authors suggested that, "Reduced fetal weights may have been secondary to the decreased maternal feed consumption observed at this dose level. Because treated females were consuming significantly less feed than control females, the fetal effects noted for rabbits (especially the post-implantation loss and decreased fetal weights) may have been due to dietary deprivation, as opposed to a direct effect by the test article."

Fetuses of the high-dose dams also had significantly greater numbers of external morphological and skeletal abnormalities compared to controls. The authors suggested that the observed fetal effects "were probably the result of dietary deprivation, maternal toxicity, or both, rather than a direct teratogenic effect of the test article" (Henwood et al. 1997). It was concluded that the NOAEL for developmental toxicity for intravenously administered MCT/LCT in rats was the high dose of 4.28 g lipid/kg bw/day, while that for rabbits was 1.00 g/kg bw/day. Since MCT constituted 75% of the test article, the NOAEL for developmental toxicity for intravenously administered MCT in rats was 3.21 g lipid/kg bw/day, while that for rabbits was 0.75 g/kg bw/day.

6.4.4. Genetic Toxicity

In a study conducted for the Food and Drug Administration, Brusick (1976) reported on the potential mutagenicity of octanoic acid in a bacterial reverse mutation assay using tester strains *Saccharomyces cerevisiae* D4 and *Salmonella typhimurium* TA1535, TA1537 and TA1538. According to a report by Traul et al. (2000), the octanoic acid exhibited no mutagenic activity either with or without metabolic activation.

The genetic toxicity of tricaprylin (a synthetic triacylglycerol with all 3 fatty acids as octanoic acid) was assessed by testing its ability to induce reverse mutations in *S. typhimurium* strains TA97, TA98, TA100, and TA1535 (NTP 1994). Tricaprylin was mutagenic in *S. typhimurium* strain TA1535 in the presence of hamster or rat S9, but only at very high concentrations (6,666 to 16,666 µg/plate). No mutagenic activity was detected in strains TA97, TA98,or TA100, when treated with tricaprylin with or without metabolic activation.

6.4.5. *In Vitro* Studies

In an *in vitro* study of the hematologic toxicity of MCT and LCT, Beau et al. (1997) obtained bone marrow samples from 6 apparently healthy adults, 5 men and 1 woman, aged 23-41 years (mean age = 28 years) and cultured them with emulsions of either LCT (from soybean oil) or a 50:50 MCT/LCT mixture for 14 days at triglyceride concentrations of 0, 0.5, 1, 2.5, 5, and 10 mg/ml. Both formulations, as compared to the control, significantly inhibited colony formation of human bone marrow cells; the MCT/LCT mixture was significantly more toxic to erythroid burst-forming units than was LCT alone. However, no relationship was reported between triglyceride concentration and bone marrow culture changes; further, *in vivo* toxicity to bone marrow cells is believed to result from accumulation of incompletely oxidized LCT. For these reasons, the authors suggested that "Clinical implications . . . should be drawn with caution."

6.4.6. Conclusions from Toxicity Studies

The toxicity of MCT—as well as the synthetic triacylglycerol tricaprylin—has been assessed in acute and repeated-dose studies in chicks, mice, rats, rabbits, dogs, sows, and minipigs. In most of these studies, the NOAEL was the highest dose tested, which ranged from 3 to 20 g/kg bw/day. The NTP (1994) study of tricaprylin was an exception, finding evidence of toxicity at 10 ml/kg bw/day (equivalent to 9.5 g/kg bw/day). Symptoms included decreased weight gain, lethargy, ataxia, dyspnea, and increased mortality. The NTP suggested that the decreased weight gain was likely due to the rapid oxidation of the fatty acids in triacylglycerol and consequent non-deposition of fat, while the other symptoms were viewed as "consistent with severe ketosis." Henwood et al. (1997) reported a developmental toxicity study in rats and rabbits in which the NOAEL for rats was the higher dose tested; adverse fetal effects were reported at the high dose in rabbits. However, in this study the MCT was administered by intravenous injection, which makes its extrapolation to oral administration uncertain. Further, the authors attributed most or all of the developmental effects to feed deprivation as the rabbits receiving the high dose of intravenous MCT consumed significantly less feed than did control or low-dose rabbits.

All studies of acute oral toxicity of MCT and a number of the repeated-dose studies, including the NTP study of tricaprylin, used gavage administration rather than dietary admixtures. The problems with gavage administration of very viscous MCT test articles were discussed in some detail by Le Bar et al. (2015), who noted that, "It has been established that a gavage administration of an oil-based formulation is associated with greater toxicity than a gavage administration of an aqueous-based formulation," and attributed the adverse effects of MCT administered to minipigs by gavage as "likely related to the aspiration of the viscous

dosing material." It is not clear to what extent the method of administration influenced some or all of the adverse effects reported in other gavage studies.

Similarly, the NTP (1994) observed that, "Increased dietary fat resulting from the use of oil gavage vehicles can alter the incidence of certain spontaneous neoplasms in rats and, thus, acts as a confounding factor in evaluating a chemical for potential toxicity and carcinogenicity." The NTP (1994) compared the effects of corn oil, safflower oil, and tricaprylin and concluded that, "These studies demonstrate that safflower oil and tricaprylin do not offer significant advantages over corn oil as a gavage vehicle in long-term rodent studies. Corn oil, safflower oil, and tricaprylin each caused hyperplasia and adenomas of the exocrine pancreas, decreased incidences of mononuclear cell leukemia, and reduced incidences or severity of nephropathy in male F344/N rats."

After reviewing the literature available at that time, Traul et al. (2000) concluded that, "The data strongly suggest that MCTs would pose little or no risk from toxicity when consumed [by humans] as a supplement in a balanced diet at levels up to 15% of the dietary calories or about 50% of the dietary fat."

Table 2. Toxicity Studies.					
Reference	**Study Design & Objective**	**Animal Model**	**Source & Description of Test Article**	**Dose & Duration of Feeding**	**Findings**
Acute Oral Toxicity					
Anony-mous 1977 (reported by Traul et al. 2000)	Acute oral toxicity; 14-day obser-vation	10 Wistar rats (5 of each sex)	MCT with 50-65% octanoic and 30-45% decanoic acid	5 g/kg bw	No adverse observations, abnormal gross pathology findings at necropsy, or deaths were reported at the tested dose.
Elder 1980	Acute oral toxicity	Female mice and male rats	MCT with varying proportions of octanoic and decanoic acids not further described	12.5 to 25 ml/kg bw (approx.. = 23.8 g/kg bw) in mice; 18.0 & 36.0 ml/kg bw (approx. = 34.2 g/kg bw) in rats	Mice: At 25 ml/kg bw, lethargy and ataxia were observed within 10 minutes of dosing and dyspnea within 1 hour, but all animals appeared asymptomatic 24 hours after administration and there was no mortality. Mice: With doses ranging from 12.5 to 25.0 ml/kg bw, ataxia, lethargy and dyspnea were observed within 15 minutes, progressing in some animals to full loss of activity by 1 hour. At doses of 20.0 and 25.0 ml/kg bw, 3 of 15 animals died within 48 hours, while surviving animals were reported to be asymptomatic by 72 hours. The authors reported that the oral LD50 for female mice was greater than 25.0 ml/kg bw. Rats: doses of 18.0 and 36.0 ml/kg bw did not result in any clinical signs or mortality and no significant findings were reported at necropsy; the oral LD50 for male rats was determined to be greater than 36.0 ml/kg bw.
Jenner et al. 1964	Acute oral toxicity of free octanoic acid; 14-day observation	10 young adult Osborne-Mendel rats (5 of each sex) after over-night fast	Free octanoic acid	Doses not reported	Animals were fasted for 18 hours prior to administration of octanoic acid by gavage. Signs of depression and diarrhea were reported, and the calculated oral LD50 for octanoic acid was 10.08 mg/kg bw.

Table 2. Toxicity Studies.					
Reference	**Study Design & Objective**	**Animal Model**	**Source & Description of Test Article**	**Dose & Duration of Feeding**	**Findings**
Klimmer 1971 (reported by Traul et al. 2000)	Acute oral toxicity; 10-day observation	Fasted male Wistar rats	MCT with 50-65% octanoic and 30-45% decanoic acid	4.5 to 36.0 ml/kg bw	No toxic effects were reported during the 10-day observation period or at necropsy, but animals receiving 18.0 and 36.0 ml/kg consumed less feed and excreted softer feces for the first 2 days.
Lewis and Palanker 1977 (reported by Traul et al. 2000)	Acute oral toxicity; 14-day observation	10 Wistar rats (5 of each sex)	MCT with 50-65% octanoic and 30-45% decanoic acid	5 g/kg bw	No adverse observations, abnormal gross pathology findings at necropsy, or deaths were reported.
Palanker 1976a (reported by Traul et al. 2000)	Acute oral toxicity; 14-day observation	10 Wistar rats (5 of each sex)	MCT with 50-65% octanoic and 30-45% decanoic acid	5 g/kg bw	No adverse observations, abnormal gross pathology findings at necropsy, or deaths were reported.
Palanker 1976b (reported by Traul et al. 2000)	Acute oral toxicity; 14-day observation	10 Wistar rats (5 of each sex)	MCT with 50-65% octanoic and 30-45% decanoic acid	5 g/kg bw	No adverse observations, abnormal gross pathology findings at necropsy, or deaths were reported.
Poole 1977 (1) (reported by Traul et al. 2000)	Acute oral toxicity	Tyler's Original strain mice	MCT with 50-65% octanoic and 30-45% decanoic acid	5.0, 10.0, 20.0 or 25.0 ml/kg bw	Clinical signs were not reported, but there were no deaths. In a second study with 25.0 ml/kg bw, lethargy and ataxia occurred within 10 minutes after administration and dyspnea was noted in some animals within 1 hour. All animals were reported to be asymptomatic at the end of the first day, but no necropsy observations were reported.

Table 2. Toxicity Studies.					
Reference	**Study Design & Objective**	**Animal Model**	**Source & Description of Test Article**	**Dose & Duration of Feeding**	**Findings**
Poole 1977 (2) (reported by Traul et al. 2000)	Acute oral toxicity	Tyler's Original strain mice	MCT with >65% octanoic acid	12.5, 20.0, or 25.0 ml/kg bw	Transient ataxia, lethargy, dyspnea and diuresis occurred within 15 minutes in the mid- and high-dose groups, and complete loss of activity occurred within 2 hours, followed by recovery, in several animals in the high-dose group. Two animals that received 20.0 ml/kg bw and one animal that received 25.0 ml/kg bw died. All symptoms disappeared in the survivors by the end of day 3, but no necropsy observations were reported.
Repeated Dose Oral Toxicity					
Harkins and Sarett 1968	Chronic oral toxicity—47 weeks	6 groups of Wistar rats, 15 sex/group	MCT (with ~75% octanoic and ~25% decanoic acid), oleo oil, butter fat, coconut oil, corn oil, or safflower oil	40% of calories for 47 weeks; MCT intake = 9 g/kg bw/day	The mean weight gain for rats fed the MCT diet was not significantly different from those for the other diets except the coconut oil diet, which resulted in greater weight gain. The groups did not differ in mortality; organ weights of the liver, kidney, spleen, heart, adrenals, and testes were similar in all groups, and histological examination of the liver and intestine showed no marked differences. Although the oil influenced the fatty acid composition of epididymal and carcass fat, little octanoic or decanoic acid was incorporated into tissue fat, indicating, according to the study authors, that these fatty acids "are rapidly metabolized to smaller units." Male rats consuming MCT had significantly lower blood cholesterol levels than those consuming the other fats, but female rats exhibited no difference; rats of both sexes had significantly lower concentrations of liver lipids when receiving MCT than when consuming diets with the other fats. The type of fat consumed had no significant effect on absorption of fat, protein, or calcium, nor on the histology of the liver or intestine. The results showed that the MCT diet supported normal growth with no reported adverse effects. The NOAEL was the only tested dose, 9 g/kg bw/day.

Table 2. Toxicity Studies.					
Reference	**Study Design & Objective**	**Animal Model**	**Source & Description of Test Article**	**Dose & Duration of Feeding**	**Findings**
Kaunitz et al. 1958	Chronic oral toxicity—12 months with a reproduction phase	46 5-week-old male Sherman albino rats	Fractionated coconut oil and reconstituted triacylglycerol from saturated fatty acids of 6-12 carbons to create MCT; the distribution of individual fatty acids was not reported	Dietary concentration of 20% (approx. = 15 g/kg bw/day) for 10 to 12 months	No overt toxicity was reported and there was no difference in survival between the two groups (17 of 23 rats receiving lard and 19 of 23 rats receiving MCT survived to termination at 10, 11, or 12 months). Rats absorbed 98.5% of the MCT and 97.7% of the lard in their diets. Rats fed MCT gained 15% less weight than did those receiving lard. Rats fed the MCT diet had TC levels significantly lower than rats on the lard diet. The authors concluded that, "Among male rats maintained on diets containing 20% lard or 20% MCT and .09% linoleic acid for 18 months no differences were observed between the groups other than the depressed body weight and lowered serum cholesterol levels of the group fed MCT."
Klimmer 1971 (1) (reported by Traul et al. 2000)	30-day oral toxicity	10 weanling male Wistar rats	MCT with 50-65% octanoic and 30-45% decanoic acid	1 or 3 ml/day (7.56 or 21.38 ml/kg bw/day) for 30 days	The volume of the gavage remained constant as the rats grew, and thus the low dose decreased over the course of the study from 7.56 to 3.58 ml/kg bw/day while the high dose declined from 21.3 to 10.8 ml/kg bw/day. No toxic or adverse effects on weight gain or urinalysis values were reported, although during the first 5-7 days of the trial there were transitory reductions in food intake and other digestive disturbances such as diarrhea.

Table 2. Toxicity Studies.					
Reference	**Study Design & Objective**	**Animal Model**	**Source & Description of Test Article**	**Dose & Duration of Feeding**	**Findings**
Klimmer 1971 (2) (reported by Traul et al. 2000)	90-day oral toxicity	Groups of 20 male and 20 female rats	MCT with 50-65% octanoic and 30-45% decanoic acid	0, 10,000 or 50,000 ppm in 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 both esterified and non-esterified fatty acids, which were all within the normal range. At necropsy, the absolute and brain-weight-relative weights of the liver, kidney, adrenal gland, thyroid gland, gonads, and brain of the rats fed the MCT were not different from controls. Traul et al. (2000) concluded that this study showed that feeding MCT did not increase triglyceride levels or induce a hyperlipidemic condition and reported that the NOAEL for MCT in the diet in this study was 50,000 ppm (5% dietary concentration), approximately equivalent to 3750 mg/kg bw/day.

Table 2. Toxicity Studies.					
Reference	**Study Design & Objective**	**Animal Model**	**Source & Description of Test Article**	**Dose & Duration of Feeding**	**Findings**
Le Bars et al. 2015	Subacute (6-week) oral toxicity by gavage	3 Göttingen® minipigs/sex/ group, aged 4 months and weighing 7.1-9.0 kg (males) and 7.1-9.7 kg (females)	Miglyol 812® (MCT with 57% octanoic, 41.4% decanoic, and 0.6% dodecanoic acid)	0.5 or 2 ml/kg bw/day (equivalent to 0.48 or 1.9 g/ kg bw/day)	No deaths occurred in any group. Tremors were observed in 2 of 3 males and 1 of 3 females in the low-dose group and in all 3 males and 1 female in the high-dose group; other clinical signs were observed sporadically, but all were transient. No significant or toxicologically meaningful effects were reported in feed consumption, bodyweight, ophthalmology, cardiovascular endpoints, hematological or coagulation parameters, or organ weights. Minipigs of both sexes receiving MCT showed a significant increase in serum TAG and a decrease in BUN; males had increased serum total and LDL cholesterol. Chronic bronchiolo-alveolar inflammation was observed in 2 of the 3 high-dose males and 1 high-dose female. Although not all animals were affected and there was no dose-effect relationship, these effects were regarded by the authors as related to the administration of MCT at 2 ml/kg bw/day. The authors concluded that "the oral administration of Miglyol 812® for six consecutive weeks induced some adverse effects in the minipig. . . . the dosing volume and/or concentration of Miglyol 812® for subchronic oral toxicity studies should be limited in the minipig." It should be noted, however, that the authors conceded that the observed adverse effects were due to gavage dosing and aspiration of a viscous material rather than to toxicity. After observing that "the main findings noted in this study were observed in the lung," they went on to explain: "These pulmonary lesions are considered to represent local effects, secondary to the aspiration of the dosing material. It has been demonstrated that oral gavage administration, even with small volumes, can result in passive gavage related-reflux. . . . An important risk factor for the occurrence of gavage related-reflux is the viscosity of the test formulation. It has been established that a gavage administration of an oil-based formulation is associated with greater toxicity than a gavage administration of an aqueous-based formulation. . . . The diffuse lesions observed in the lung were considered to be likely related to the aspiration of the viscous dosing material, Miglyol 812®, during the dosing procedure."

Table 2. Toxicity Studies.					
Reference	**Study Design & Objective**	**Animal Model**	**Source & Description of Test Article**	**Dose & Duration of Feeding**	**Findings**
Matulka et al. 2009	Subchronic (90-day) dietary oral toxicity study	16 beagle dogs of each sex aged 1-6 years (4 dogs/sex/group	MCT (not further described)	0, 5, 10, or 15% dietary concentration of MCT for 90 days	There was no mortality or significant differences in bodyweights or bodyweight changes among the groups; although some palatability effects were seen early in the study with the MCT-containing diets, there were no overall differences in feed intake. Findings from the physical and ophthalmic examinations were unremarkable and there were no significant differences in hematological indices. With regard to biochemistries, the mid- and high-dose dogs of both sexes showed significant increases in BUN and decreases in urine volume and concomitant increased specific gravity. The authors concluded that, "Based on the findings from this 91-day MCT feeding study, there are no indications of toxicological effects in dogs fed up to 15% MCT in the diet. . . . Therefore, a logical conclusion from this study is that the no-adverse-effects level (NOAEL) for the canine is 15% MCT in feed." This is approximately equivalent to 30 g MCT/day. Assuming mean weights of 10-11 and 9-10 kg for adult male and female beagles, respectively, the NOAEL is equivalent to approximately 3 g MCT/kg bw/day for both sexes.
Roth and Shapiro 1981 (reported by Traul et al. 2000)	Subacute (21-day) dietary oral toxicity	12 7-day-old Single Comb White Leghorn male chicks	MCT with 50-65% octanoic and 30-45% decanoic acid	0% or 16% dietary admixture for 3 weeks	The chicks consuming the MCT diet had significantly reduced body weight gain and reduced muscle weight. These effects were reportedly due to the reduced feed consumption by chicks receiving the high fat diet, and all mortality was attributed to starvation and not the consumption of MCT. Slight subcutaneous edema was observed in 3 treated birds, but heart fluid volume was minimal in all chicks from treated and control birds and there was no evidence of an edematous condition. The absence of "chick edema factor" was determined by the reported absence of hydropericardium, hydroperitoneum, or subcutaneous edema at necropsy. The necropsy did not reveal any abnormal changes in liver or kidney. The authors concluded that the results of this study showed that "MCT does not contain chick edema factor" and that "MCT is not toxic to chicks." (The 16% dietary concentration, which may be regarded as the NOAEL, is approximately equivalent to a dose of 20 g/kg bw/day.)

Table 2. Toxicity Studies.					
Reference	**Study Design & Objective**	**Animal Model**	**Source & Description of Test Article**	**Dose & Duration of Feeding**	**Findings**
NTP 1994	Chronic (2-year) oral toxicity and carcino-genicity gavage study	60 7-week-old male F344/N rats (15/group)	Tricaprylin (trioctanoin), a synthetic triacylglycerol in which all 3 fatty acids are octanoic acid	0, 2.5, 5 or 10 ml/kg bw/day 5 days/week for 2 years	The survival of rats receiving 10 ml tricaprylin/kg bw/day was lower than that of controls. Clinical findings of dyspnea, ataxia, and lethargy following dosing were recorded for 50 of the 60 animals receiving 10 ml tricaprylin/kg bw/day. However, the animals generally recovered prior to the next daily dosing, and the incidence of clinical findings declined during the second half of the study. The mean body weight of the high-dose group was significantly lower than that of the controls throughout the study. There were significant dose-related increased incidences of pancreatic exocrine hyperplasia and adenoma and the incidence of proliferative lesions of the forestomach increased significantly with dose. The incidence of nephropathy was significantly decreased in high-dose rats, and the severity of nephropathy decreased with increasing dose. In high-dose group rats, the incidence of mononuclear cell leukemia was significantly decreased. Although the study report did not identify a NOAEL, since there were no significant differences in any of the observed parameters between the control and the 2.5 ml/kg bw/day group, the NOAEL for tricaprylin is 2.5 ml/kg bw/day or about 2.37 g/kg bw/day.

Table 2. Toxicity Studies.					
Reference	**Study Design & Objective**	**Animal Model**	**Source & Description of Test Article**	**Dose & Duration of Feeding**	**Findings**
Sellers et al. 2005	Subacute (4-week) oral toxicity by gavage	6-8-week-old male and female Wistar Han IGS rats (15 rats/sex/dose)	Miglyol 812® (MCT with 57% octanoic, 41.4% decanoic, and 0.6% dodecanoic acid)	10 ml/kg bw/day for 4 weeks	There was no mortality. MCT consumption resulted in soft and/or mucoid stooling lasting 0-8 days in males and 0-5 days in females. Feed intakes of males and females consuming MCT were only 66% and 84% of that of control animals, and bodyweight gain was significantly reduced in both sexes. Feed-efficiency ratios were not reported, but the reduced weight gain appears to be attributable to reduced feed intake. Hematology parameters were not affected, but significant increases were reported in serum TAG and TC; serum protein, globulins, and BUN were significantly reduced but remained within the normal historical ranges. Alveolar histiocytosis was significantly more frequently reported in rats gavaged with MCT than in control rats, but this condition is common in older rats and in often seen in gavage studies; the authors attributed it to aspiration of the dosing material. Both absolute and relative weights of thymus were significantly lower in males and females receiving MCT, but were not accompanied by any histological changes in the thymus. All reported effects during dosing were not observed during recovery. The authors did not report any adverse effects indicating toxicity, suggesting a NOAEL of 10 ml/kg bw/day, the only dose tested, equivalent to 9.5 g/kg bw/day."

Table 2. Toxicity Studies.					
Reference	**Study Design & Objective**	**Animal Model**	**Source & Description of Test Article**	**Dose & Duration of Feeding**	**Findings**
Webb et al. 1991	Subacute (28-day) oral toxicity feeding study	120 male and female weanling Crl:CD BR Sprague-Dawley rats(15 rats/sex/ group) aged 4 weeks, weighing 88-107 g (M) and 83-96 g (F)	Caprenin, a mixed-chain MCT/LCT consisting of octanoic (23.2%), decanoic (26.6%) and docosanoic (45%) acids	0, 5, 10, or 15% dietary concentration for 28 days	There was no mortality. Female weight gain was similar across all groups, but male rats had dose-dependently lower weights when consuming diets containing caprenin. Both males and females in the high-dose caprenin group consumed significantly more feed than did control rats. Absolute liver weights of caprenin-group male rats were significantly lower than those of controls, but relative weights did not differ. Absolute cecum weights were significantly reduced in low- and mid-dose male rats, but not in high-dose males or in females. Kidneys and testes of males in all treatment groups showed significant increases in relative weights, but no differences were reported in absolute weights. Female rats in the high-dose group had significantly increased absolute and relative kidney weights. ALT values were significantly increased at all dose levels in females and in the high-dose males. Elevated platelet counts were reported in high-dose males and hemoglobin levels in mid-dose females. No gross pathological lesions were reported. Diet had no effect on the fat content of the heart, but rats consuming caprenin rather than corn oil had significant dose-related reductions in the fat content of the liver. The authors concluded that "An important outcome of the 28-day feeding study with rats was the absence of any toxicity for levels of [caprenin] ranging up to 15% of the diet (83% of total dietary fat)." The NOAEL for caprenin in this study is the highest dietary concentration tested, 15%, equivalent to 14.5 g/kg bw/day in males and 16.4 g/kg bw/day in females.

Table 2. Toxicity Studies.					
Reference	**Study Design & Objective**	**Animal Model**	**Source & Description of Test Article**	**Dose & Duration of Feeding**	**Findings**
Webb et al. 1993	Subchronic (90-day) oral toxicity feeding study	200 male and female weanling Crl:CD BR Sprague-Dawley rats (25 rats/sex/ group) aged 4 weeks and weighing 71-98 g (M) and 68-88 g (F)	Caprenin, a mixed-chain MCT/LCT consisting of octanoic (23.2%), decanoic (26.6%) and docosanoic (45%) acids and MCT not further described	0, 5.23, 10.23 or 15.00% dietary concentration of caprenin, and 11.2% dietary concentration of MCT for 91 days	There were no treatment-associated deaths and clinical observations revealed no findings that were uncommon or at increased frequency for animals of this type and age, with the exception of increased incidences of tail desquamation in animals receiving MCT. There were no differences in body weights or body weight gains across all groups. In the groups fed caprenin, females had lower absolute liver weights while male rats exhibited lower relative liver weights; both of these observations were attributed to reduced deposition of fat in the livers. Males on the 15% caprenin diet consumed significantly more feed and females consumed significantly less feed than other dietary groups. Differences in clinical chemistry and hematologic values across all groups were considered to be not toxicologically significant. The necropsy evaluation included granular renal observations for caprenin high-dose females; this observation had no histopathological correlates and was considered to be related to renal changes (nephrocalcinosis) that occur normally in female rats. No other gross or histopathological findings were reported. There were no significant differences among groups in the fat content of the hearts, livers, or perirenal fat pads. The NOAEL for caprenin was the maximum tested dietary concentration of 15%, equivalent to 13.2 and 14.6 g/kg bw/day for males and females, respectively. For MCT, the NOAEL was the single dietary concentration tested, 11.2% of the diet, equivalent to approximately 9.2 g/kg bw/day.

Table 2. Toxicity Studies.					
Reference	**Study Design & Objective**	**Animal Model**	**Source & Description of Test Article**	**Dose & Duration of Feeding**	**Findings**
Developmental and Reproductive Toxicity					
Azain et al. 1993	Develop-mental toxicity study (survival of neonatal piglets)	54 Yorkshire x Landrace or Yorkshire x Duroc sows	MCT, not further described	0 or 10% dietary concentration from gesta-tion day 91 through lac-tation day 7	There was no effect of treatment on average sow weight at any time and no difference in the number of live piglets at birth. Survival was significantly improved in litters from sows fed MCT relative to litters from sows fed the control diet. The greatest improvement in survival was observed in pigs weighing less than 900 g. 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 MCT. The authors concluded that "MCT may provide a practical means to improve survival rates."

Table 2. Toxicity Studies.					
Reference	**Study Design & Objective**	**Animal Model**	**Source & Description of Test Article**	**Dose & Duration of Feeding**	**Findings**
Harkins and Sarett 1968	Reproductive toxicity study	Young adult male and female McCollum-Wisconsin rats (numbers not reported)	MCT with 75% octanoic and 25% decanoic acid	0 or 40% dietary concentration from 3 weeks prior to mating, through the F_1 generation and to weaning of the F_2 pups	The feeding groups did not differ in the number of pups (F_1 generation) per litter or birthweights, but the mean weight of the pups at weaning was significantly higher for dams receiving the high-fat diets (which did not differ) than those on the low-fat diet. There was no difference in mortality during lactation between the MCT and oleo-oil diets. The F_1 rats were raised on the diets fed their dams, and the weights at 49 and 105 days did not differ between the two high-fat groups. The F_1 females were mated after 3 weeks and the F_2 pups were raised to the age of 63 days. There were no differences among groups in F_2 generation litter sizes or birthweights, At weaning (21 days), the mean bodyweights were significantly higher among the pups whose dams were receiving a high-fat diet (MCT or oleo oil) than those fed a low-fat diet. In both the F_0 and F_1 generation dams, the diet had no effect on the quantity of milk secretion or on the total fat content. The milk of dams ingesting MCT contained a significantly higher proportion of octanoic and decanoic fatty acids than did the milk of those fed oleo oil (23.3% v. 8.0%), but the proportion was substantially less than the fraction of octanoic and decanoic acids in the MCT. The authors suggested that, "It is apparent that the rats fed MCT were required to synthesize a large portion of the fatty acids secreted in the milk fat," but concluded that "the MCT diet also supported normal reproduction, as indicated by litter size and number."

Table 2. Toxicity Studies.					
Reference	**Study Design & Objective**	**Animal Model**	**Source & Description of Test Article**	**Dose & Duration of Feeding**	**Findings**
Henwood et al. 1997	Intravenous develop-mental toxicity (MCT may be used in enteral or parenteral nutrition)	77 mated Crl:CD BR rats weighing 150-200 g (24-28 rats/group) and 45 mated Hra:(NZW)SPF rabbits aged 5.5-6.5 months and weighing 3,300-4,446 g (15 rabbits/group)	3:1 mixture of MCT and LCT	0, 1, or 4.28 g/kg bw/day	High-dose rats showed a dose-dependent increase in tail lesions due to extravasation of the test article into perivascular areas. There was a "trend toward" an increasing incidence of necropsy findings in the high-dose rats, but no single finding was significant. All female rats, with the except of one control rat, were pregnant and had at least one viable fetus/litter. There were no significant differences in pre- or post-implantation loss, in the percentage of live or resorbed fetuses, or in their mean bodyweights; there were no dead fetuses in any group. There were no test-article-related fetal external, visceral, or skeletal observations in rats. In the rabbit study, there were no test-article-related maternal effects, and all pregnant animals had at least one viable fetus. However, the high-dose rabbits had a significantly higher proportion of resorptions/litter than the controls, and mean fetal bodyweights were significantly lower. Fetuses of the high-dose dams had significantly greater numbers of external morphological and skeletal abnormalities compared to controls. The authors suggested that the observed fetal effects "were probably the result of dietary deprivation, maternal toxicity, or both, rather than a direct teratogenic effect of the test article." The NOAEL for developmental toxicity for intravenously administered MCT/LCT in rats was the high dose of 4.28 g lipid/kg bw/day, while that for rabbits was 1.00 g/kg bw/day. Since MCT constituted 75% of the test article, the NOAEL for developmental toxicity for intravenously administered MCT in rats was 3.21 g lipid/kg bw/day, while that for rabbits was 0.75 g/kg bw/day.

Table 2. Toxicity Studies.					
Reference	**Study Design & Objective**	**Animal Model**	**Source & Description of Test Article**	**Dose & Duration of Feeding**	**Findings**
Kaunitz et al. 1958	Feeding study of develop-mental and reproductive toxicity	46 5-week-old Sherman albino rats (23 rats/sex/ group)	MCT, not further described	0 or 20% dietary concentration for 10, 11, or 12 months	When treated male rats were mated at 9 months of age with either treated or control females, all males were found to be equally fertile and litters were normal with respect to number and weight. However, the lactation performance of females on MCT diets was poor, as shown by lower survival and growth rates of the pups. The pups from females that had been maintained on the MCT diet were maintained on MCT + 0, 0.09, or 2% linoleic acid. Half of the males on the 0% linoleic supplement died; however, all survivors and all rats of the other groups grew to weights which correlated with the amount of linoleic acid given. Surviving male rats were mated again with untreated females at 18 months, and fertility was 87% among males that had received MCT and 69% among those that had received lard. The incur-poration of 20% MCT had no adverse effects on reproduction.

6.5. Nutrition Studies

6.5.1. Animal Studies

These studies are discussed below and summarized in Table 3.

The effect of a single oral load of 1.5 g of MCT, LCT, or 0.9%-NaCl control on ketonemia in 114 Wistar rats (38 rats per group) weighing 261±2 g was reported by Bach et al. (1977). The MCT tested comprised 50.5% octanoic acid, 48.0% decanoic acid, and 1.0% dodecanoic acid. Blood samples were obtained at intervals throughout the first 100 minutes after gavage dosing. Blood analyses suggested that the level of ketone bodies, β-hydroxybutyrate (β-OHB), and acetoacetate in the blood did not vary after LCT treatment, but was significantly increased after the administration of MCT. β-OHB levels reached a peak approximately 15 min after MCT ingestion, at which time blood levels reached approximately 700 nmol/ml and were approximately fivefold higher than those of the rats in the LCT and control groups. Plasma TAG and non-esterified fatty acids were unaffected by MCT but significantly elevated by ingestion of LCT. In order to study the effect of MCT quantity on changes in ketone-body levels, a second experiment with 32 Wistar rats with a mean weight of 241±4 g compared results of dosing with 0, 0.119, 0.235, 0.292, 0.348, or 0.460 g MCT. No dose-response relationship was reported with ketone bodies, plasma TAG, or non-esterified fatty acids. The authors concluded that "ketogenesis depends principally on the amount of fatty acids incorporated into lipids synthesized by the liver."

Baba et al. (1982) reported on the thermogenic effect and fat deposition for MCT and LCT in Sprague-Dawley rats. Fifteen male rats weighing 270±12 g were fitted with gastrostomy tubes; animals were fed twice daily through the tube; 7 rats received a diet comprising 25% MCT and 2.5% corn oil and 8 rats were fed an isocaloric diet with 26% LCT (corn oil) for 6 weeks. The fatty acid content of the MCT was not described. The feeding was planned to provide 150% of caloric need based on the *ad libitum* feed consumption of matched rats. No significant adverse effects were reported. Animals fed the MCT diet had significantly lower levels of dissectible fat, which was attributed to higher resting and maximal norepinephrine-stimulated O_2 consumption and metabolic rate. Liver fat and blood glucose values were comparable between the two groups. The authors concluded, "Overfeeding with a diet containing MCT as the major source of fat resulted in significantly lower body weight and body fat as compared with an isocaloric diet containing only LCT," attributable to "increased metabolic rate and thermogenesis."

Geleibter et al. (1983) reported on a study in which gastrostomy tubes were implanted in 16 male Sprague-Dawley rats weighing 304±7.3 g. Two weeks after surgery, 9 rats were placed on a diet comprising 26% LCT (corn oil) and 7 rats were assigned a diet with 2.5% corn oil and 25% MCT (3% hexanoic, 68% octanoic, 28% decanoic, and 1% dodecanoic acid) for 6 weeks. The feeding provided 150% of caloric need based on the *ad libitum* feed consumption of matched rats. During week 6 of the study, rats were monitored for total spontaneous physical activity over a 24-hr period; no differences between the 2 groups were reported. The MCT-fed rats gained 20% less weight and had fat deposition weighing 23% less than LCT-fed rats. Serum insulin levels and the weights of carcass protein and water did not differ between the 2 feeding groups. The authors cited a chyluria patient in their hospital who had received MCT "as an

exclusive source of fat for more than 15 years without producing side effects, and the patient has remained extremely lean," in concluding that "an MCT diet deserves investigation as a potential adjunct in the dietary prevention of human obesity."

Edens and Friedman (1984) reported a study wherein normal and diabetic rats were fed diets with escalating levels (5% to 15% to 25%) of either corn oil (LCT) or MCT (3% hexanoic, 68% octanoic, 24% decanoic, and 5% dodecanoic acid) to compare effects produced. Male Sprague-Dawley rats were randomized into 2 groups, streptozotocin-induced diabetes (n = 16) and control (n = 22). Three weeks after the administration of streptoztocin, the bodyweights of control rats ranged from 345 to 446 g while the diabetic rats weighed 272 to 404 g. Eleven normal rats and 8 diabetic rats were assigned to receive either LCT or MCT for 6 weeks, 2 weeks at each dose level. It was reported that caloric intake was more rapidly adjusted in the normal and diabetic rats fed the MCT-containing diet than those receiving LCT. It was reported that both normal and diabetic LCT-fed rats preferred high dietary fat, whereas MCT-fed rats did not. Plasma TAG and glycerol were decreased in both normal and diabetic rats fed the MCT-containing diet. However, plasma ketones in the normal rats were increased whereas there was no apparent effect on plasma ketones in the diabetic rats. The authors concluded that these findings "confirm previous findings in normal animals and furnish new data on the effect of MCT feeding in diabetic rats" and "demonstrate an effect of MCT feeding on the regulatory response to increased dietary fat content which may be the result of the unique metabolic consequences of MCT feeding."

Webb and Sanders (1991) reported on the digestion and absorption of caprenin, a mixed-chain MCT/LCT consisting of octanoic (23.2%), decanoic (26.6%), and docosanoic (45%) acids in male and female Sprague-Dawley rats. Twenty rats of each sex aged 9-12 weeks weighing 274.3±19.2 g (M) and 202.3±10.8 g (F) were implanted with thoracic duct catheters; after at least 24 hours, each rat was gavaged with 5 ml of a solution providing 0 fat or 1.5 g of caprenin, coconut oil, or peanut oil. Lymph was collected over at least 24 hours to obtain at least 17 ml fluid and analyzed for fatty acid composition. While 74% of the peanut oil and 51% of the coconut oil was recovered in lymph, only 10% of the caprenin was recovered—specifically, 3.9% of the octanoic acid, 17.8% of the decanoic acid, and 11.2% of the docosanoic acid were recovered. The authors reported that "There was no evidence of significant rearrangement of the positions of fatty acids on glycerol during digestion and absorption," and concluded that caprenin is "qualitatively digested, absorbed, and processed like any dietary fat or oil that contains medium-chain and very long-chain fatty acids."

Chanez et al. (1991) reported on the metabolic effects of a diet containing MCT in 240 individually-housed male Wistar CF rats weighing 150-180 g. In the first experiment, 152 rats were divided into 3 feeding groups with 48 rats/group; 8 control rats were euthanized at time zero to provide baseline samples of blood and liver. The feeding groups included one group that received a low-fat diet and two groups fed diets with 32% of energy from fat, either MCT (0.2% hexanoic, 56.2% octanoic, 43.1% decanoic, and 0.5% dodecanoic acid) or LCT (corn oil). Feed intake was measured every 2 days and body weight every 4 days; 8 animals per group were killed after 1, 4, 8, 15, 25, and 45 days. Blood was analyzed for glucose, TAG, glycerol, TC, free fatty acids, and ketone body concentrations. Samples of liver were tested for glycogen, lactate,

pyruvate, malate, citrate, and ketone bodies, and activities of malic enzyme, glucose-6-phosphate dehydrogenase, phosphoenol-pyruvate carboxykinase, ATP-citrate lyase, fatty-acid synthase, and acetyl-CoA carboxylase. The remaining carcass was assayed for water, fat, and nitrogen.

In the second experiment (Chanez et al. 1991), 88 rats were assigned to receive the low-fat diet (n = 72 rats) or either the LCT or MCT diet (n = 8 rats each) for 3 weeks, after which 8 of the rats on the low-fat diet and all 16 rats on the two moderate-fat diets were killed for analyses of blood and liver. The remaining 64 low-fat-diet rats were divided into 2 groups of n = 32 and received either the low-fat diet or the MCT diet; 8 rats from each group were killed after 2, 7, 14, and 21 days and their blood and livers were assayed.

Rats fed the MCT diet had significantly 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 reported between the LCT and MCT groups with respect to plasma glucose, TAG, free fatty acids, or liver weight; hepatic glycogen levels were 50% lower in the LCT group. Blood ketone body concentrations in the MCT-fed rats were significantly greater than LCT-fed rats only on day 1, but were comparable on days 4, 8, 15, 25 and 45. The mean blood ketone body values on day 1 in the MCT group were approximately 100 mmol/ml blood. The authors concluded:

> "This study shows that in rats, long-term consumption of a diet in which MCT constitutes 30% of metabolizable energy did not change energy intake, body weight gain, energy and nitrogen retention, or lipid deposition. Moreover, no alteration in hepatic metabolites or in both blood and hepatic ketone body concentrations was observed. . . In addition, a high activity in the hepatic lipogenic enzymes was observed, showing that MCT per se had no inhibitory effect on the activity of these enzymes. These observations suggest an adaptation of the rat to the long-term consumption of such a diet containing MCT at a level not reached in human feeding" (Chanez et al. 1991).

Table 3. Studies of MCT in Animals.					
Reference	**Research Objective**	**Animal Model**	**Source & Description of Test Article**	**Dose & Duration of Feeding**	**Findings**
Baba et al. 1982	Compare the thermogenic effect and fat deposition for MCT and LCT given by gavage	15 male Sprague-Dawley rats weighing 270±12 g	MCT, no further described	0 or 25% dietary concentration for 6 weeks	No significant adverse effects were reported. Animals fed the MCT diet had significantly lower levels of dissectible fat, which was attributed to higher resting and maximal norepinephrine-stimulated O_2 consumption and metabolic rate. Liver fat and blood glucose values were comparable between the two groups.
Bach et al. 1977	Ketogenesis of MCT and LCT	Wistar rats	MCT with 50.5% octanoic, 48.0% decanoic, and 1.0% dodecanoic acid	1.5 g in a single oral load	Blood analyses suggested that the level of ketone bodies, β-OHB, and acetoacetate in the blood were increased by MCT, although no dose-response relationship was observed with ketone bodies. β-OHB levels reached a peak 15 min after MCT ingestion, when blood levels reached 700 nmol/ml and were fivefold higher than those of the rats in the LCT and control groups. Plasma TAG and non-esterified fatty acids were unaffected by MCT but significantly elevated by ingestion of LCT. The authors concluded that "ketogenesis depends principally on the amount of fatty acids incorporated into lipids synthesized by the liver."

Table 3. Studies of MCT in Animals.					
Reference	**Research Objective**	**Animal Model**	**Source & Description of Test Article**	**Dose & Duration of Feeding**	**Findings**
Chanez et al. 1991	Study metabolic effects of a diet with MCT	240 male Wistar CF rats weighing 150-180 g	MCT with 0.2% hexanoic, 56.2% octanoic, 43.1% decanoic, and 0.5% dodecanoic acid	0 or 32% of energy for 45 days	Rats fed the MCT diet had depressed levels of plasma TC, weight gain was decreased by 21%, and energy retention was decreased by 26% relative to 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, TAG, free fatty acids, or liver weight; hepatic glycogen levels were 50% lower in the LCT group. Blood ketone body concentrations in the MCT-fed rats were greater than LCT-fed rats only on day 1, but were comparable on days 4, 8, 15, 25 and 45. The authors concluded: "This study shows that in rats, long-term consumption of a diet in which MCT constitutes 30% of metabolizable energy did not change energy intake, body weight gain, energy and nitrogen retention, or lipid deposition. Moreover, no alteration in hepatic metabolites or in both blood and hepatic ketone body concentrations was observed. . . In addition, a high activity in the hepatic lipogenic enzymes was observed, showing that MCT per se had no inhibitory effect on the activity of these enzymes. These observations suggest an adaptation of the rat to the long-term consumption of such a diet containing MCT at a level not reached in human feeding."
Edens and Friedman 1984	Regulatory response of normal and diabetic rats to MCT and LCT	38 male Sprague-Dawley normal (n = 22) and diabetic (n = 16) rats	MCT with 3% hexanoic, 68% octanoic, 24% decanoic, 5% dodecanoic acid	Escalating levels (5% to 15% to 25% dietary concentration for 6 weeks (2 weeks at each dose level)	Caloric intake was more rapidly adjusted in the normal and diabetic rats fed the MCT-containing diet than those receiving LCT. Both normal and diabetic LCT-fed rats preferred high dietary fat, whereas MCT-fed rats did not. Plasma TAG and glycerol were decreased in both normal and diabetic rats fed the MCT-containing diet. However, plasma ketones in the normal rats were increased whereas there was no apparent effect on plasma ketones in the diabetic rats. The authors concluded that these findings "demonstrate an effect of MCT feeding on the regulatory response to increased dietary fat content which may be the result of the unique metabolic consequences of MCT feeding."

Table 3. Studies of MCT in Animals.					
Reference	**Research Objective**	**Animal Model**	**Source & Description of Test Article**	**Dose & Duration of Feeding**	**Findings**
Geleibter et al. 1983	Compare the thermogenic effect and fat deposition for MCT and LCT given by gavage	16 male Sprague-Dawley rats weighing 304±7.3 g (9 rats in test group, 7 rats in control)	MCT with 3% hexanoic, 68% octanoic, 28% decanoic, 1% dodecanoic acid	0 or 25% dietary concentration for 6 weeks	The MCT-fed rats gained 20% less weight and had fat deposition weighing 23% less than LCT-fed rats. Serum insulin levels and the weights of carcass protein and water did not differ between the 2 feeding groups. The authors cited a chyluria patient in their hospital who had received MCT "as an exclusive source of fat for more than 15 years without producing side effects, and the patient has remained extremely lean," in concluding that "an MCT diet deserves investigation as a potential adjunct in the dietary prevention of human obesity."
Webb and Sanders 1991	Study the digestion and absorption of caprenin	40 male and female Sprague-Dawley rats (5 rats/sex/group) weighing 274.3±19.2 g (M) and 202.3±10.8 g (F)	Caprenin, a mixed-chain MCT/LCT consisting of octanoic (23.2%), decanoic (26.6%) and docosanoic (45%) acids	0 or 1.5 g in a single gavage administration	Only 10% of the caprenin was recovered in lymph— 3.9% of the octanoic acid, 17.8% of the decanoic acid, and 11.2% of the docosanoic acid were recovered. The authors reported that "There was no evidence of significant rearrangement of the positions of fatty acids on glycerol during digestion and absorption," and concluded that caprenin is "qualitatively digested, absorbed, and processed like any dietary fat or oil that contains medium-chain and very long-chain fatty acids."

6.5.2. Human Studies

6.5.2.1. Preterm and Low Birthweight Infants

These studies are discussed below and summarized in Table 4.

Tantibhedhyangkul and Hashim (1971) enrolled 34 preterm infants (sex and health status not reported) with birthweights of 1,332-1,980 g in a randomized, prospective, controlled study of fat absorption from infant formula containing MCT; blinding was not reported. The infants were divided into 3 groups to receive formula with 0% (n = 13), 40% (n = 10), or 80% (n = 11) of the fat in the form of MCT (not further described) beginning during the first week of life and continuing throughout their hospital stay, 30 to 60 days. Urine and 5-day stool samples were collected during the second week and again during the last week of hospitalization to measure the amount of unabsorbed fat. Replacement of LCT with MCT significantly improved fat absorption in the first and last weeks, from 73-76% in the 0%-MCT group to 92-93% in the 40%-MCT and 97-97% in the 80%-MCT groups. Although specific data were not reported, the authors reported that nitrogen absorption was significantly higher in the 80%-MCT group than in the other 2 groups, and that both MCT groups had "striking" diminutions in stool volume and frequency. They concluded that, "The results of these studies clearly indicate that the absorption of fat and nitrogen can be improved in premature infants by administration of formulas that contain MCT." No adverse effects from ingestion of MCT by preterm infants were reported.

Tantibhedhyangkul and Hashim (1975) reported the same study again, but in this report they discussed nitrogen absorption and excretion in more detail. Iron absorption during the first and last weeks, respectively, was 91.7 and 91.3% in the control group, 91.1 and 91.8% in the 40%-MCT group, and 95.2 and 95.9% in the 80%-MCT group, which was significantly higher than in the other two groups. Nitrogen excretion data showed significantly lower excretion in the two MCT groups than in the control—early and late urinary nitrogen 9.3 and 15.9 mg/mg creatinine in the 0%-MCT group vs.6.8 and 8.1 mg nitrogen in the 40%-MCT group and 7.0 and 8.3 mg nitrogen/mg creatinine in the 80%-MCT group. Ketosis was also reported to not occur in the infants of this study, although two infants in the 80% MCT group exhibited blood ketone levels of 4.5 mg/100 ml. The authors stated that, "There were no ill effects observed in either MCT group except that two premature infants in the 80% MCT group had some degree of clinically manifest but transient abdominal distension," and concluded that, "This study demonstrates that premature infants thrive on MCT-containing formulas without any untoward effects."

Tantibhedhyangkul and Hashim (1978) reported the same study yet again, this time focusing on the effects of MCT on absorption of calcium and magnesium in preterm infants. The urine samples collected during the second week of life and during the final week of hospitalization were analyzed for calcium and magnesium levels. The mean calcium absorption, expressed as a percent of dietary calcium, was significantly increased (approximately 50-100%) in both of the MCT groups relative to control; magnesium absorption was significantly increased (approximately 50%) in the 80% MCT group relative to control. There was no significant difference in urinary calcium or magnesium excretion, expressed per unit of urinary creatinine, among the three groups. The authors concluded, "The improvement in calcium and magnesium

absorption correlated well with fat absorption. Thus, MCT-containing formulas may be useful for feeding premature infants early in life in an attempt to improve both calorie and divalent cation absorption."

A randomized study with enterally-fed low-birth-weight infants investigating the effect of MCT on 25-hydroxy vitamin D serum levels and the absorption and retention of calcium and phosphorus was reported by Huston et al. (1983). Twenty healthy preterm infants (sex not reported) with birthweights under 1,500 g received a high calcium- and vitamin D-containing enteral formula that contained 50% of its fat as either MCT (not further described) or LCT. All infants began enteral feedings by 7 days of age, and feedings were advanced to a goal of 150 ml/kg bw/day. Blood samples were obtained within the initial 24 hours of the feedings, within 24 hours of reaching a feeding level of 140 ml/kg bw/day, and at two additional time points after reaching the target consumption of 150 ml/kg bw/day. Serum data for 25-hydroxy vitamin D showed no significant differences between the two groups at any of the sampling periods. Approximately 1 week after attaining full feeding volumes, a 96-hour metabolic balance study was initiated. Calcium and phosphorus levels were determined in stools, urine, and blood and these data were used to compare intake, absorption and retention for the MCT and LCT groups. There were no significant differences in the absorption or retention of calcium or phosphorus between the two groups. There were also no differences between the MCT and LCT groups in growth rate (weight gain, gain in crown-heel length, or increase in occipital-frontal circumference) and no reported adverse effects from either formula.

Because low-birthweight infants do not digest fat well and lose substantial energy in feces, Whyte et al. (1986) compared the energy balance of such infants fed formula with lipids comprising either 4% or 46% (by weight) MCT, the remainder being LCT. (The MCT was described as containing only octanoate and decanoate esters, but the ratio was not reported.) Both formulas contained about 44 g fat/L and so the MCT contents were 1.8 and 20.5 g/L. Fifteen low-birthweight infants (mean birthweight = 1380±340 g) were enrolled, with mean gestational age of 31±2 weeks and age at enrollment of 15±4 days; sex was not reported. The study was a prospective, randomized, double-blind, crossover design; each infant received each formula for 5 days in random order, with a 3-day balance period after each feeding period. The amounts of formula fed were based on each infant's morning bodyweight. Urine and stool were collected over each balance period and energy expenditure was measured twice during each balance period by the oxygen and carbon-dioxide content of expired air.

No differences were reported in energy intake, energy loss in stool, energy expenditure, or weight gain between the two formulas. No adverse effects were reported, but the authors concluded that, "We were unable to demonstrate any benefit in terms of energy or nitrogen balance attributable to the addition of high levels of medium-chain triglyceride in formula designed for growing LBW infants."

In a prospective, randomized, double-blind crossover trial (Hamosh et al. 1991), nine enterally-fed preterm infants (gestational age at birth 25-33 weeks, mean = 29.1±0.88 weeks; birth weight 750-1,740 g, mean = 1,157±110 g) aged 0.5-6.9 (mean = 3.13±0.71) weeks at enrollment, were randomly assigned to receive two formulas, each for 1 week. The formulas

were a standard enteral formula with LCT constituting 86% of the lipid and an MCT formula in which MCT accounted for 50% of the lipid content. The MCT formula was described as containing 1.3% hexanoic, 33.6% octanoic, 15.3% decanoic, and 7.4% dodecanoic fatty acid, with the remainder a variety of LCFA. Anthropometric measures and gastric aspirates were taken at the beginning and end of each feeding period and stools were collected during the last 3 days of each feeding period.

No differences were reported between the 2 formulas in fat absorption or growth, but the lipase activity in gastric aspirates was significantly higher in infants receiving standard formula than in those receiving high-MCT formula. The authors reported that, "The MCT are mainly used as an energy source and are not utilized for growth," and concluded that "It is doubtful that addition of large amounts of MCT (40-50% of total fat) would improve fat absorption in premature infants," and suggested that formulas should contain about 10-15% MCT.

The effect of MCT- and LCT-containing formulas on metabolic rate; nitrogen and fat balances; macronutrient oxidation; calcium, phosphorus. and magnesium balances; and plasma levels of 1,25-dihydroxy vitamin D and alkaline phosphatase in healthy preterm infants weighing less than 1,600 g at birth was reported by Sulkers et al. (1992a, 1992b). Twenty-eight infants with mean gestational age of 31.4±1.9 weeks and mean birthweight of 1192.1±208.5 g (sex not reported) were randomized before the introduction of oral feeding to receive either pre-term formula in which 38.0% of the fat consisted of medium-chain fatty acids (C6:0 – C10:0; MCT group, n = 15) or a formula with a similar total fat content but containing only 6% medium-chain fatty acids (LCT group; n = 13). Feedings were gradually introduced on day 7 by continuous nasogastric lavage until an intake of 150 ml/kg/day was reached at days 16-19. Two 72-hour balance studies were carried out within approximately 2 weeks of achieving the target intake level, which involved analyses of blood, stools, and urine for nitrogen, fat, calcium, phosphorus, magnesium, and 1,25-dihydroxy vitamin D.

There were no differences between groups in weight gain, metabolic rate, nitrogen absorption or excretion, or plasma levels of 1,25-dihydroxy vitamin D or alkaline phosphatase, but fat absorption was significantly higher in the MCT group than in the LCT group, 88% vs. 79%. The absorption and retention of calcium and magnesium were also approximately 10-20% higher in the MCT group; absorption of phosphorus was the same in the two groups, but excretion was significantly higher in the LCT group, possibly compensation caused by the lower calcium absorption. The authors concluded that "MCTs have no advantage in the routine feeding regimen of otherwise healthy, growing preterm infants" but "might have a place in the treatment of younger and more immature preterm infants."

Wu et al. (1993) investigated the effect of MCT in enteral formulas for low-birthweight infants on gastrointestinal (GI) tolerance, fat absorption, plasma ketone levels, and urinary dicarboxylic acid excretion. Sixty infants, low-birthweight (≤1500 g) but otherwise healthy, were enrolled and randomly assigned to receive one of 4 formulas containing 0% (n = 16), 17% (n = 15), 34% (n = 14), or 50% (n = 15) of the total fat as MCT; they remained on their assigned formula for 18-22 days. Anthropometric data were collected on the first day of enteral feeding and on the first and last days of full feedings. GI tolerance was assessed daily based on the

occurrence of emesis and abdominal distention. A 48-hour balance study was conducted during which stools, urine, and blood were collected.

There were no differences among the formulas in formula intake, growth, fat absorption, or blood chemistry with the exception of plasma β-OHB, a marker of ketosis, which was significantly higher in the infants consuming the formula with 50% MCT than in those consuming formula with no MCT. Urinary dicarboxylic acid, formed by the oxidation of MCFA, also increased significantly with increasing levels of MCT. Tolerance for the formulas was excellent: formula intolerance was reported in only 2 cases, one in the MC-free formula group and the other in the low-MCT (17%) group. The authors concluded that "fat absorption and GI tolerance were not affected by different MCT levels (0 to 50% of the total fat)."

Nonoxidative metabolism of MCTs was examined in six preterm infants fed a standard preterm formula containing 38% fat as MCTs (Carnielli et al. 1994). All infants were on full oral feeds and gaining weight at the start of the study. Formula was administered at 4 weeks of age via an orogastric tube using a syringe pump. The study consisted of an oral primed constant-rate infusion of (^{13}C)-octanoate and the measurement of ^{13}C-enriched individual fatty acids in plasma triacylglycerols by gas chromatography-isotope ratio mass spectrometry (GC-IRMS). A significant incorporation of the label was detected in plasma triacylglycerols (10% ± 4.5% of the enrichment diet). Incorporation of the label was also detected in myristic and palmitic acids (4.8% ± 2.5% and 7.8% ± 4.1% of the enrichment diet, respectively). Octanoic and decanoic acids in plasma were only 7.3% and 32% respectively of the mol % content of the diet and myristic and palmitic acids were increased by 225% and 343%. These data provide some evidence that medium chain fatty acids may be elongated to LCFAs, but the majority of MCTs are oxidized. Furthermore, these data suggest that MCTs can impact metabolism of other fatty acids. No treatment-associated adverse effects were reported.

In a prospective, randomized, blinded, controlled trial, Romera et al. (2004) reported on metabolic and energy balances in healthy preterm infants enterally given formula containing non-protein energy supplements for 11 days. Thirty preterm neonates (gestational age <31 weeks and birth weight <1,500 g), 14 males and 16 females, were enrolled. The mean gestational age of the enrolled infants was 29.4 weeks and their mean birth weight was 1151.4 g; their mean age at the beginning of the study was 25.2 days. While the control group (n = 8 infants) received standard preterm formula enterally (150 ml/kg bw/day), 3 test groups (7 or 8 infants each) received formula supplemented with different blends of MCT and dextrinomaltose providing an additional 23 kcal/kg bw/day; the blends were in ratios of 33:66, 66:33, and 85:15. (The MCT source was a commercial product but was not described.) Bodyweight, length, head circumference, skinfold thicknesses, oxygen consumption, and carbon dioxide production were measured at baseline and on day 11; stool and urine samples as well as samples of capillary blood were taken every 2 days. Urine was tested for nitrogen, stools for fat and protein, and blood for glucose.

Energy supplementation resulted in significantly increased fat accretion, but with little difference between supplementation primarily MCT or primarily carbohydrate. There were no differences in growth, energy expenditure, nitrogen retention, or fat and protein excretion. No

adverse effects were reported associated with consumption of MCT by preterm infants. The authors concluded that, "Excess nonprotein energy is stored as fat regardless of its source (fat or carbohydrate). High caloric and medium-chain triglyceride intake in otherwise healthy growing preterm infants does not promote nitrogen retention."

Table 4. Studies of MCT in Infants.					
Reference	**Study Design & Objective**	**Subjects**	**Source and Characteristics of Test Article**	**Dose & Duration**	**Results**
Hamosh et al. 1991	Prospective, randomized, double-blind crossover trial of the effect of MCT on fat absorption in enterally-fed preterm infants	9 enterally-fed preterm infants (mean gestational age at birth 29.1±0.88 weeks; mean birth weight 1,157±110 g), mean age at enrollment 3.13±0.71) weeks	MCT with 1.3% hexanoic, 33.6% octanoic, 15.3% decanoic, and 7.4% do-decanoic acid	50% of lipids for 1 week	No differences were reported between the 2 formulas in fat absorption or growth, but the lipase activity in gastric aspirates was significantly higher in infants receiving standard formula than in those receiving high-MCT formula. Observing that, "The MCT are mainly used as an energy source and are not utilized for growth," the authors concluded that "It is doubtful that addition of large amounts of MCT (40-50% of total fat) would improve fat absorption in premature infants," and suggested that formulas should contain about 10-15% MCT.
Huston et al. 1983	Prospective, randomized, parallel-group study of the effect of MCT on 25-hydroxy vitamin D serum levels and absorption and retention of Ca and P	20 healthy preterm infants with birthweights under 1,500 g	MCT, not further described	50% of lipids until discharge	25-hydroxy vitamin D showed no significant differences between the two groups at any of the sampling periods. There were no significant differences in the absorption or retention of Ca or P between the two groups. There were also no differences between the MCT and LCT groups in growth rate (weight gain, gain in crown-heel length, or increase in occipital-frontal circumference) and no reported adverse effects from either formula.

Table 4. Studies of MCT in Infants.					
Reference	**Study Design & Objective**	**Subjects**	**Source and Characteristics of Test Article**	**Dose & Duration**	**Results**
Romera et al. 2004	Prospective, randomized, blinded, controlled trial of metabolic and energy balances in healthy preterm infants enterally given formula containing non-protein energy supplements	30 preterm neonates (14 males and 16 females) with gestational age <31 weeks and birth weight <1,500 g	MCT not further described	0, 7.6, 15.2, or 19.6 kcal/kg bw/day for 11 days	Energy supplementation resulted in significantly increased fat accretion, but with little difference between supplementation primarily MCT or primarily carbohydrate. There were no differences in growth, energy expenditure, nitrogen retention, or fat and protein excretion. No adverse effects were reported associated with consumption of MCT by preterm infants.
Sulkers et al. 1992a, 1992b	Prospective, randomized, controlled trial of metabolic and energy balances in healthy preterm infants	28 healthy preterm infants with mean gestational age of 31.4±1.9 weeks and mean birthweight of 1192.1 ± 208.5 g	MCT not further described	6 or 38% of lipid content for 19+ days	There were no differences between groups in weight gain, metabolic rate, nitrogen absorption or excretion, or plasma levels of 1,25-dihydroxy vitamin D or ALP, but fat absorption was significantly higher in the MCT group than in the LCT group. Absorption and retention of Ca and Mg were 10-20% higher in the MCT group; absorption of P was the same in the two groups, but excretion was significantly higher in the LCT group. The authors concluded that "MCTs have no advantage in the routine feeding regimen of otherwise healthy, growing preterm infants" but "might have a place in the treatment of younger and more immature preterm infants."

Table 4. Studies of MCT in Infants.					
Reference	**Study Design & Objective**	**Subjects**	**Source and Characteristics of Test Article**	**Dose & Duration**	**Results**
Tantibhedhy-angkul and Hashim 1971 Tantibhedhy-angkul and Hashim 1975 Tantibhedhy-angkul and Hashim 1978	Prospective, randomized, controlled study of fat absorption from infant formula containing MCT	34 preterm infants with birthweights of 1,332-1,980 g	MCT not further described	0, 40, or 80% of lipid content for 30-60 days	1971 report: Replacement of LCT with MCT improved fat absorption in the first and last weeks. Nitrogen absorption was higher in the 80%-MCT group and both MCT groups had "striking" diminutions in stool volume and frequency. The authors concluded that, "The results of these studies clearly indicate that the absorption of fat and nitrogen can be improved in premature infants by administration of formulas that contain MCT." No adverse effects from ingestion of MCT by preterm infants were reported. 1975 report: Iron absorption was higher in the 80%-MCT group than in the other two groups. Nitrogen excretion was lower in the two MCT groups than in the control. The authors stated that, "There were no ill effects observed in either MCT group except that two premature infants in the 80% MCT group had some degree of clinically manifest but transient abdominal distension," and concluded that, "This study demonstrates that premature infants thrive on MCT-containing formulas without any untoward effects." 1978 report: Ca absorption was increased in both of the MCT groups relative to control; Mg absorption was increased in the 80% MCT group relative to control. There was no difference in urinary Ca or Mg excretion among the three groups. The authors concluded, "The improvement in calcium and magnesium absorption correlated well with fat absorption. Thus, MCT-containing formulas may be useful for

Table 4. Studies of MCT in Infants.					
Reference	**Study Design & Objective**	**Subjects**	**Source and Characteristics of Test Article**	**Dose & Duration**	**Results**
					feeding premature infants early in life in an attempt to improve both calorie and divalent cation absorption."

Table 4. Studies of MCT in Infants.					
Reference	**Study Design & Objective**	**Subjects**	**Source and Characteristics of Test Article**	**Dose & Duration**	**Results**
Whyte et al. 1986	Prospective, randomized, double-blind, crossover trial of effect of MCT and LCT on energy balance in LBW infants	15 LBW infants (mean birthweight = 1380±340 g) with mean gestational age of 31±2 weeks and 15±4 days old at enrollment	MCT described as containing only octanoate and decanoate esters	4 or 46% of lipid content (1.8 or 20.5 g/L) for 5 days	No differences were reported in energy intake, energy loss in stool, energy expenditure, or weight gain between the two formulas. No adverse effects were reported, but the authors concluded that, "We were unable to demonstrate any benefit in terms of energy or nitrogen balance attributable to the addition of high levels of medium-chain triglyceride in formula designed for growing LBW infants."
Carnielli et al,.1994	Prospective, open label, single-arm trial to determine conversion of MCFA to LCFA in LBW infants	6 LBW infants (mean birthweight 1.5 ±0.12 kg) with mean gestational age of 31.8 ±1.7 weeks); infants administered study formula when on full oral feeding for at least 10 days	MCT described as containing 65% octanoic acid and 35% decanoic acid	Standard preterm infant formula with 38% of fat as MCT; Formula and [^{13}C]-octanoate tracer administered via orogastric tube; blood samples collected 6 hours following isotope administration	Incorporation of the dietary [^{13}C]-octanoic acid in plasma TG (10.0% ± 4.5% of the enrichment of the diet) was observed. A noticeable incorporation of the label was detected in myristic and palmitic acids (4.6% ± 2.5% and 7.8% ± 4.1% of the octanoic enrichment of the diet). The plasma TG fatty acid profile differed markedly from the diet. Octanoic and decanoic acids in plasma were only 7.3% and 32%, respectively, of their mol% content of the diet, and myristic and palmitic acids were increased by 225% and 343%. "Our findings demonstrate for the first time *in vivo* the conversion of octanoic acid into long-chain saturated fatty acids." No adverse effects associated with treatment were reported.

Table 4. Studies of MCT in Infants.					
Reference	**Study Design & Objective**	**Subjects**	**Source and Characteristics of Test Article**	**Dose & Duration**	**Results**
Wu et al. 1993	Prospective, randomized, parallel group study of the effect of MCT in enteral formulas for LBW infants on tolerance, fat absorption, plasma ketones, and urinary dicarboxylic acid	60 LBW infants (≤1500 g) but otherwise healthy	MCT not further described	0, 17, 34, or 50% of lipid for 18-22 days	There were no differences among the formulas in formula intake, growth, fat absorption, or blood chemistry with the exception of plasma β-OHB, which was higher in the infants consuming the formula with 50% MCT than in those consuming formula with no MCT. Urinary dicarboxylic acid, formed by the oxidation of MCFA, also increased significantly with increasing levels of MCT. Tolerance for the formulas was excellent: formula intolerance was reported in only 2 cases, one in the MC-free formula group and the other in the low-MCT (17%) group. The authors concluded that "fat absorption and GI tolerance were not affected by different MCT levels (0 to 50% of the total fat)."

6.5.2.2. Healthy Term Infants

Five growth studies of infant formula containing MCT up to 21 g/L have been published (Table 5). All studies followed similar designs with healthy, full-term, exclusively formula-fed infants enrolled around 14 days of age and followed to about 4 months or 112 days of age. No study made mention of safety concerns or unexpected adverse events that would indicate safety issues with any of the infant formulas studied. Age-appropriate growth was observed in all studies, ranging from 25.9-29.8 g/day when reported, indicating the MCT-containing infant formulas studied are nutritionally adequate to support growth of healthy infants. Adverse events reported were mainly related to gastrointestinal issues such as loose stools, which are not uncommon in infant growth studies. High drop-out rates were observed; however, MCT-containing infant formulas are hypoallergenic extensively hydrolyzed or amino acid-based formulas which tend to have a bitter taste and a distinct odor. As growth studies involve healthy infants who do not necessitate the use of such formulas, high drop-out rates are expected in such studies. Data from these growth studies in healthy infant populations exclusively fed MCT-containing infant formulas indicate the safe use of MCT in infants.

Table 5. Growth Studies of MCT-Containing Infant Formula.					
Reference	**Study Design & Objective**	**Subjects**	**Source and Characteristics of Test Article**	**Dose & Duration**	**Results**
Fields et al. 2016	Prospective double-blind controlled study of 2 infant formulas evaluating growth and tolerance in healthy term infants receiving a new whey-based EHF compared to infants receiving commercially available casein-based EHF	282 exclusively formula-fed healthy term infants enrolled at 14±3 days of age	Test: Extensive HA infant formula, 100% whey extensively hydrolyzed with 49% of fat from MCT (17 g/L) Control: Pregestimil infant formula, extensively hydrolyzed casein-based formula with 55% of fat from MCT (21 g/L)	Exclusively formula-fed *ad libitum* from 2 weeks to 4 months of age	The control group had a significantly higher overall drop-out rate than the test group (56% vs 41%), with a significantly higher number of drop-outs caused by adverse events (26% vs 15%). Mean intake was 26.36 oz/d in the Test group (13 g/d MCT) and 27.26 oz/d in the Control group (17 g/d MCT). Mean daily gains in weight (g/d) were significantly greater in the Test group as compared to the Control, though the difference was within 3 g/d of each other (27.95 g/d versus 25.93 g/d). Length and head circumference were significantly greater in the Test group. Serum albumin and plasma amino acids drawn at 3 months of age were within normal limits for both groups. 846 AEs were reported throughout the course of the study (39% in the Test and 61% in the Control group). In the Test group, 14% of AEs were reported to be 'definitely' or 'probably' related to the formula compared to 29% in the Control group. The most frequently reported AEs included loose stools, cough, and nasal congestion. 15 participants (6 Test, 9 Control) had an SAE. All were deemed to be unrelated or unlikely to have a relationship to the study product. The authors concluded, "The 100% whey-based hypoallergenic EHF containing Bifidobacterium lactis and medium chain triglycerides supported growth of healthy infants."

Table 5. Growth Studies of MCT-Containing Infant Formula.					
Reference	**Study Design & Objective**	**Subjects**	**Source and Characteristics of Test Article**	**Dose & Duration**	**Results**
Corkins et al, 2015	Prospective double-blind controlled study of 2 amino acid-based infant formulas evaluating growth and tolerance in healthy term infants	225 exclusively formula-fed healthy term infants enrolled at 0-17 days of age	Test: Alfamino amino acid-based infant formula with 43% of fat from MCT (15 g/L) Control: Neocate amino acid-based infant formula with 33% of fat from MCT (10 g/L)	Exclusively formula-fed *ad libitum* from 0-17 days to 4 months of age	The drop-out rate was 47% in the Test group and 40% in the Control group. For the Test group, 34% of drop-outs were due to AEs , and 38% of drop-outs in the Control group were due to AEs. Mean intake was 29.34 oz/d in the Test group (13 g/d MCT) and 28.75 oz/d in the Control group (9 g/d MCT). Mean daily gains in weight (g/d) were similar between the groups (27.99 g/d in the Test group, 27.30 g/d in the Control). Length gains per day were similar between groups, though infants in the Control group were significantly longer at 14, 84, and 112 days of age. There were no differences in head circumference. Serum albumin and plasma amino acids drawn at 3 months of age were within normal limits for both groups. There was no difference in the total number of AEs (nonserious or serious) reported between the groups. In the ITT population, 11 infants assigned to Control formula and 17 infants assigned to Test formula reported an AE of loose stools. The authors concluded, "This study shows that the new AAF (amino acid-based formula) supports growth similarly to a commercially available AAF and is another suitable option for infants who may require the use of an AAF."

Table 5. Growth Studies of MCT-Containing Infant Formula.					
Reference	**Study Design & Objective**	**Subjects**	**Source and Characteristics of Test Article**	**Dose & Duration**	**Results**
Borschel et al. 2014	Masked, controlled, randomized, parallel growth and tolerance trial of healthy term infants during the first 4 months of life.	195 exclusively formula-fed healthy singleton full-term infants enrolled at 0-9 days of age	Test: Alimentum extensively hydrolyzed casein-based powder (PWD) with 33% of fat from MCT (12 g/L) Control: Alimentum extensively hydrolyzed ready-to-feed formula (RTF) with 33% of fat from MCT (13 g/L)	Exclusively formula-fed *ad libitum* from 0-9 days to 4 months of age	The drop-out rate was 29% in the PWD group and 30% in the RTF group. For the PWD group, 17% of these drop-outs were due to formula intolerance, and for the RTF group, 21% were due to formula intolerance. Formula intake was significantly greater in the RTF group. Mean intake was 522 ml at the start of study and 879 ml at 112 days of age in the PWD group (6-11 g/d MCT) and ranged from 592-1002 ml from start to end of study in the RTF (8-13 g/d MCT). Mean weight gain from 14 to 112 days of age of the RTF and PWD groups were similar (28.9 g/day vs 28.4 g/day). There were no differences between groups in length or head circumference. Infants fed PWD had significantly fewer stools per day compared to infants fed RTF throughout the study. There were no differences in stool consistency, vomit, or spit-up. There were 90 AEs and 7 SAEs reported in the PWD group compared 97 AEs and 6 SAEs in the RTF group. The authors stated, "In conclusion, the current study demonstrates that both the RTF and PWD forms of this extensively hydrolyzed casein-based formula are safe, support normal growth, and were well tolerated by young infants."

Table 5. Growth Studies of MCT-Containing Infant Formula.					
Reference	**Study Design & Objective**	**Subjects**	**Source and Characteristics of Test Article**	**Dose & Duration**	**Results**
Harvey et al. 2014	Prospective double-blind randomized controlled trial of healthy full-term infants (0-15 days). Publication also addresses separate hypoallergenicity study conducted in infants/children with cow's milk protein allergy where subjects completed double-blinded placebo-controlled food challenges with the study formulas.	115 healthy, full-term, exclusively formula-fed infants aged from birth to 15 days	Test: Neocate amino acid based infant formula with synbiotic blend and 33% of fat from MCT Control: Neocate amino acid based infant formula with 4% of fat from MCT Overall fat content was not stated in publication.	Exclusively formula-fed *ad libitum* from 0-15 days to 4 months of age	The drop-out rate was 46% in the Test group, with 44% of these drop-outs due to AEs. The drop-out rate was 32% in the Control group, with 56% of these drop-outs due to AEs. Reported mean formula intake was 11.8 ounces per day for Test and 11.2 ounces per day for the Control. Mean number (± SD) of formula exposure days was 75.5 ± 51.5 for Test and 79.1 ± 45.4 for Control. There was no statistically significant difference in weight gain, achieved length, or achieved head circumference between the two formula groups for the ITT and PP analyses. Minimal differences were observed in stool characteristics and GI symptoms throughout the study. The Test group reported more watery/soft pudding–like and more yellow/brown stools. More infants had at least one reported AE in the Control (49 (88%)) compared to the Test (37 (63%)) group. The majority of AEs were categorized as mild and unrelated to the formulations. Six SAEs were reported to be unrelated to the formula intake and one in the Control group (dehydration) was reported as 'possibly' related by the investigator. The most frequent type of AE considered formula-related were classified as GI disorders. The authors concluded, "These studies demonstrate that an AAF with synbiotics is safe and well tolerated and promotes normal growth when fed to healthy full-term infants as the sole source of nutrition and is hypoallergenic in subjects with CMA."

Table 5. Growth Studies of MCT-Containing Infant Formula.					
Reference	**Study Design & Objective**	**Subjects**	**Source and Characteristics of Test Article**	**Dose & Duration**	**Results**
Borschel et al. 2013	Masked, controlled, randomized, parallel growth study of healthy singleton infants aged 0-9 days	213 healthy, full-term exclusively formula-fed infants aged from 0-9 days at enrollment	Test: Elecare amino acid based infant formula with 33% of fat as MCT (11 g/L) Control: Nutramigen extensively hydrolyzed infant formula with no MCT	Exclusively formula-fed *ad libitum* from 0-9 days to 112 days	The drop-out rate was 39% in the Test group, with 64% of these drop-outs due to formula intolerance. The drop-out rate was 35% in the Control group, with 57% of these drop-outs due to formula intolerance. Reported mean formula intake was 591 ml/d at baseline up to 894 ml at the end of the study in the Test (7-10 g MCT/d), and 564 ml/d at baseline up to 842 ml/d at the end of the study in the Control group. There were no statistically significant differences between feeding groups in mean weight or in mean weight gain (Test, 28.2 g/d; Control 28.2 g/d). There were no statistically significant differences between the groups for length or head circumference or for length gain during the study. Number of formed stools and daily number of stools were greater in the EHF group at 14 and 28 days of age. No specifics were given regarding adverse events. The authors stated, "No safety concerns emerged during this study," and concluded that the amino acid-based formula supported normal growth of infants comparable to that of infants fed an extensively hydrolyzed (Nutramigen) during the critical first 4 months of life.

6.5.2.3. Studies in Special Infant Populations

Other studies of MCT-containing infant formula have been published in which infants of special populations were administered formulas. There have been reports of MCT-containing infant formula use in study populations including infants and children with cow's milk protein allergy, diarrhea, cystic fibrosis, and other indications for which specialized infant formulas were clinically warranted. However, as the focus was not the presence of MCT in the formulas, details on the MCT content of the formula, actual formula intake, and adverse events were not consistently reported in published papers. Table 6 contains a summary of two studies (Burks et al. 2015 and Vandenplas et al. 2010) in which adverse events were reported and three studies (Borschel et al. 2014, Canani et al. 2017, and Galeano et al. 1998) in which details of adverse events were not provided. Intake data as stated within each publication are reported in Table 6. While study designs and populations are diverse in these studies, they indicate safe use of MCT-containing infant formula in non-healthy populations. No studies indicated safety issues due to the MCT content of the formula.

Table 6. Studies of MCT-Containing Infant Formula in Specific Populations of Infants and Children.					
Reference	**Study Design & Objective**	**Subjects**	**Source and Characteristics of Test Article**	**Dose & Duration**	**Results**
Burks et al., 2015	Prospective, randomized, double-blind study assessing growth of infants with cow's milk allergy using an amino acid-based formula with synbiotics and evaluating its safety in the intended population	110 infants (0-8 months) with IgE or non-IgE-mediated cow's milk allergy	Test: Neocate amino acid based infant formula with synbiotic blend and 33% of fat from MCT Control: Neocate amino acid based infant formula with 4% of fat from MCT	Fed randomized formula for 16 weeks	In the control group, there was a 16% drop-out rate, and 33% of these were due to (serious) AEs; for the test group, drop-out rate was 20%, with 55% due to (serious) AEs. Both formulas were well-tolerated. Although significant differences were found between groups for hemoglobin, hematocrit, red blood cell count, and alkaline phosphatase, all values were within reference ranges. A significantly lower percentage of subjects in the Test group needed drugs for functional GI disorders and antibacterials for systemic use. The study formula was well accepted and intake levels were comparable in both groups (data not shown). Both formulas equally supported growth according to WHO 2006 growth charts and resulted in similar increases of weight, length, and head circumference. Fecal pH, some bacterial populations, and short chain fatty acids were significantly different between groups. 43 subjects in the Test and 38 subjects in the control reported AEs, the majority of which were mild or moderate in severity. Significantly more subjects in the Test group reported diarrhea than the Control (22% vs 4%). Significantly fewer subjects in the Test group experienced infections compared to the Control (18% vs 2%). Six SAEs were reported (2 in Test, 4 in Control), none of which were related to study formula. The authors concluded that the synbiotic-containing amino acid-based formula supports normal growth that is similar to non-synbiotic containing formula.

Table 6. Studies of MCT-Containing Infant Formula in Specific Populations of Infants and Children.					
Reference	**Study Design & Objective**	**Subjects**	**Source and Characteristics of Test Article**	**Dose & Duration**	**Results**
Vandenplas et al., 2010	Prospective open-label study evaluating the nutritional adequacy of a semi-elemental formula	47 children with functional gastro-intestinal disorders suggesting enteropathy, malabsorption, or CMPA	Alfaré extensively hydrolyzed whey formula containing 40% MCT (5.1 g fat/100 kcal; approximately 14 g MCT/L)	Patients <1 year old were fed solely with the study formula for 4 weeks, and for those > 1 year, the study formula constituted at least 75% of caloric intake	Nineteen patients dropped out because they refused to drink the study formula or because the parents chose not to continue in the study, and two infants were withdrawn by the investigator due to persistent vomiting. One infant was dropped from the analysis because of lack of data on length, blood analysis or tolerance. Mean intake was 122.5 ± 38.3 ml/kg bw/day. Weight and length evolution during the 4-weeks trial were within normal range. Albumin increased, plasma amino acid levels improved, no changes in fatty acid red blood cell levels. 54 AEs were reported in 26 patients, mostly GI disorders. None of the AEs were related to the study formula. No SAEs were reported. The authors concluded that the formula "is safe and nutritionally adequate for pediatric patients with gastrointestinal disease."

Table 6. Studies of MCT-Containing Infant Formula in Specific Populations of Infants and Children.					
Reference	**Study Design & Objective**	**Subjects**	**Source and Characteristics of Test Article**	**Dose & Duration**	**Results**
Borschel et al., 2014	Two single group, prospective baseline-controlled feeding studies in which each subject served as his/her own control. One study was of infants (<12 months), the other of children (>12 months).	19 infants and 27 children with chronic diarrhea (lasting >2 weeks and ≥4 stools/day)	EleCare amino acid-based formula with 33% of fat from MCT. For infants, formula was 20 kcal/oz, containing 11 g MCT/L. For children, formula was 30 kcal/oz, containing 16 g MCT/L	Subjects were fed study formula for 80 days. Study formula provided at least 50% of energy for all subjects.	Drop-out rate for the infants was 19%, none related to AEs. Drop-out rate for the children was 5%. At the end of the study, the mean formula intake for infants was 104 kcal/kg bw/day. Mean weight was 7.53 kg. Approximate mean MCT intake for infants would have been 13 g/day at the end of the study. At the end of the study, the mean formula intake for children was 110 kcal/kg bw/day. Mean weight was 19.2 kg. Approximate mean MCT intake for children would have been 33 g/day. Infant subjects achieved significant increases in weight-for-age z-scores, significant decreases in the number of stools/day, and improvements in stool consistency. Over 80% of infant subjects achieved improvements in the clinical outcomes targeted most frequently by their physicians. Children subjects achieved significant increases in weight-for-age z-scores. Over 50% of subjects achieved improvements in clinical outcomes targeted most frequently by their physicians. There was no specific mention of AEs for either infants or children subjects. The authors concluded, "Children and infants with chronic diarrhea fed EleCare for three months displayed improvements in growth and clinical symptoms."

Table 6. Studies of MCT-Containing Infant Formula in Specific Populations of Infants and Children.					
Reference	**Study Design & Objective**	**Subjects**	**Source and Characteristics of Test Article**	**Dose & Duration**	**Results**
Canani et al., 2017	Randomized, controlled trial evaluating effects on body growth and protein metabolism of amino acid-based formula and extensively hydrolyzed whey formula in cow's-milk-allergic children compared to healthy controls	50 infants (5-12 months) with suspected cow's milk allergy (CMA), not yet on cow's milk elimination diet. 25 healthy controls included	Group 1: Neocate amino acid based infant formula with 4% of fat from MCT (1g MCT/L) until 12 months, followed by Neocate Advance (35% of fat from MCT (7g MCT/L). Group 2: Hypolac extensively hydrolyzed whey formula with no MCT Healthy controls: follow-on formula then growing-up milk without MCT after 12 months	Subjects followed for 12 months	There were no drop-outs. Energy and protein intake were similar between the CMA groups. At baseline, there was no difference in weight-for-age z-score between cow's milk allergic groups; however the healthy controls had significantly greater weight-for-age z-score at baseline. Use of both hypoallergenic formulas resulted in similar weight gain for CMA subjects during the 12-month study period. By 6 and 12 months post-enrollment, there was no difference in weight-for-age z-score in the CMA subjects compared to healthy controls. Protein metabolism biomarkers were similar between groups. AEs were not reported in the publication. The authors concluded, "Long-term treatment with AAF is safe and allows adequate body growth in children with CMA."
Galeano et al., 1998	Randomized crossover study of two 7-day periods comparing two protein hydrolysate formulas with regard to water and electrolyte losses, fat and nitrogen balance, absorbed and metabolizable energy, and weight gain	6 mal-nourished infants (1-13 months); 2 had intractable diarrhea, 4 short bowel syndrome	Alfaré extensively hydrolyzed whey formula containing 50% MCT (16 g/L) Pregestimil extensively hydrolyzed casein formula containing 41% MCT (11 g/L)	Each formula fed via continuous infusion for 7 days each. Two subjects received 50% of their calories from parenteral nutrition.	No subjects dropped out. There was no difference in energy or fat intake between the two periods. Mean daily weight gain was satisfactory (30.6 d/day on Alfaré, 25.1 g/d on Pregestimil). Tolerance was good for both formulas. There was no difference in stool weight, sodium and potassium losses, transit time, and enteral absorption of fat, carbohydrate-derived energy, and total energy. 97% of MCT were completely absorbed. Maldigested or malabsorbed carbohydrates accounted for 63% of energy loss during Alfaré feeding and 72% during Pregestimil feeding. AEs were not reported in the publication. The authors concluded that both formulas were satisfactory, and "thought should be given to reformulation with a lower concentration of carbohydrates and a higher concentration of fat."

6.5.2.4. Studies in Children

These studies are discussed below and summarized in Table 7.

Leyland et al. (1969) enrolled 13 children, 8 males and 5 females, aged 1 month to 15½ years (mean age = 6.80±4.23 years) with malabsorption in an open-label study of the effects of replacement of a portion of the dietary LCT with MCT. Five children suffered from intestinal lymphangiectasia, 3 had obstructive jaundice, 3 had pancreatic insufficiency, and 2 had abetalipoproteinemia. Daily intake of LCT was reduced while MCT was introduced gradually over a week to a final amount of 20-70 g/day; total fat supplied about 40% of daily caloric intake. The MCT oil used provided about 85% octanoic acid (C8:0) and 15% decanoic acid (C10:0). Diets were continued for 5-36 months. Fecal samples were collected daily and analyzed for lipid content.

Results were reported in groups described by the cause of malabsorption:

- Intestinal lymphangiectasia: absorption of MCT was "virtually complete" with less than 1% of the ingested MCT appearing in feces. Elimination or reduction of edema was reported in all children; effects on growth velocity were assessed in only one child, who showed improvement in height from <3rd centile to the 25th centile after 2 years.
- Obstructive jaundice: steatorrhea of LCT was gross, but was abolished by replacement of LCT by MCT. About 4% of the octanoic acid and from 7 to 23% of the decanoic acid was not absorbed. Little or no benefit in growth velocity or liver function was reported from the treatment.
- Pancreatic insufficiency: MCT diets reduced fecal lipid content, but normal values were not achieved. Little or no benefit in growth velocity or liver function was reported from the treatment.
- Abetalipoproteinemia: although MCT treatment improved fecal lipid levels, little or no benefit in growth velocity or liver function was reported from the treatment.

The authors concluded that "MCT diets controlled the steatorrhoea in all four groups of disorders. Analysis of the faecal fatty acid pattern showed that MCT absorption was somewhat impaired where bile or pancreatic lipase was deficient, but was virtually complete in intestinal lymphangiectasia and a-β-lipoproteinaemia where the intraluminar phase of fat digestion was normal. Control of steatorrhoea improved the general well-being of all the children." No adverse effects attributable to MCT treatment were reported.

Neal et al. (2009) randomized 145 children with intractable epilepsy to receive ketogenic diets based on either MCT (n = 72) or LCT (n = 73) for 12 months. The children, including 76 boys and 69 girls, were divided by age—2-6 years (n = 66), 7-11 years (n = 59), and 12-16 years (n = 20). Children on the MCT diet received 40-45% of energy from MCT, increasing up to 60%, while those on the LCT diet received about 65% of energy from fat, increasing up to 80%. (The difference in the percentage of energy from fat is due to the greater ketogenic potential of MCT over LCT and consequently a greater allowance for protein and carbohydrates.) Seizures were recorded daily, as were urinary ketone levels, while ketosis based on blood measures, diet

tolerability, height and weight, hematology, and serum biochemistry were evaluated at 3, 6 and 12 months.

Eight patients assigned to the MCT group and 12 assigned to receive LCT withdrew prior to the beginning of the dietary intervention for reasons not associated with the study (e.g., changed mind, unable to travel to the study center, seizures improved); 15 MCT patients and 10 LCT patients withdrew during the first 3 months and 17 MCT patients and 15 LCT patients withdrew after the third month. There were no significant differences at any time point between children receiving the MCT diet and those receiving LCT in the frequency of seizures. The most common side effects with both diets were constipation, vomiting, and hunger; diarrhea and abdominal pain were reported only infrequently. The only significant differences in adverse effects between the two dietary groups were a higher incidence of vomiting in the LCT group at 12 months and more frequent reports of lack of energy in the LCT group at 3 months. The authors concluded that, "This study has shown classical [LCT-based] and MCT ketogenic diet protocols to be comparable in efficacy and tolerability."

In a prospective open-label study, Lambrechts et al. (2015) reported the long-term (2-year) tolerability and effect of a ketogenic diet based on MCT as adjunct therapy in treating children with refractory epilepsy. The study enrolled 48 children and adolescents aged 1-18 years (mean age = 7.8 years) with refractory epilepsy, 32 males and 16 females; patients were excluded if there were medical contraindications such as cardiovascular disorders or metabolic acidosis. The patients included 18 children under the age of 5 years, 12 aged 5-10 years, 15 aged 10-15 years, and 3 over the age of 15. The MCT ketogenic diet was introduced over a 2-week period, beginning at 10 g MCT per day and "slowly increased to the calculated amount of MCT-fat"; unfortunately, this upper amount of MCT was not reported. Patients were evaluated at baseline, 6 weeks, and every 3 months, including seizure frequency and severity, side effects, height and body mass index, blood samples (for analysis of TC, LDL, TAG, and β-OHB), and urine (for ketone levels).

Eleven patients discontinued within 3 months due to problems with compliance or side effects such as abdominal pain and vomiting. Diarrhea and constipation were also reported during the first 3 months, but rarely later. Most withdrawals after 3 months were reportedly due to lack of perceived efficacy rather than compliance or intolerance issues. Sixteen patients remained on the MCT diet for more than a year and 11 for more than 2 years; the authors reported that 4 patients "are still maintaining the diet after 5 to 8 years." The MCT-based ketogenic diet significantly reduced seizure frequency and severity. No significant changes were reported in blood or urine measures. The authors concluded that the MCT-based ketogenic diet "is an effective therapy for children with therapy-resistant epilepsy. . . . The most invalidating side effects, especially in the first 3 months of treatment, are gastrointestinal symptoms which can usually be reduced by fine-tuning the diet."

Table 7. Studies of MCT in Children.					
Reference	**Study Design & Objective**	**Subjects**	**Source and Characteristics of Test Article**	**Dose & Duration**	**Results**
Lambrechts et al. 2015	Prospective open-label study of the long-term (2-year) tolerability and effect of a ketogenic diet based on MCT as adjunct therapy in treating children with refractory epilepsy	48 children and adolescents aged 1-18 years (mean age = 7.8 years) with refractory epilepsy; 32 males and 16 females	MCT not further described	10 g/day at start, escalating to an unreported level for 2 years	11 patients discontinued within 3 months due to problems with compliance or side effects such as abdominal pain and vomiting. Diarrhea and constipation were also reported during the first 3 months, but rarely later. 16 patients remained on the MCT diet for more than a year and 11 for more than 2 years; the authors reported that 4 patients "are still maintaining the diet after 5 to 8 years." The MCT-based ketogenic diet significantly reduced seizure frequency and severity. No significant changes were reported in blood or urine measures. The authors concluded that the MCT-based ketogenic diet "is an effective therapy for children with therapy-resistant epilepsy. . . . The most invalidating side effects, especially in the first 3 months of treatment, are gastrointestinal symptoms which can usually be reduced by fine-tuning the diet."

Table 7. Studies of MCT in Children.					
Reference	**Study Design & Objective**	**Subjects**	**Source and Characteristics of Test Article**	**Dose & Duration**	**Results**
Leyland et al. 1969	Prospective open-label study of the effects of replacement of a portion of dietary LCT with MCT	13 children (8 males and 5 females) aged 1 month to 15½ years (mean age = 6.80±4.23 years) with intestinal lymphangia-ectasia, obstructive jaundice, pancreatic insufficiency, or abetalipo-proteinemia	MCT with about 85% octanoic and 15% decanoic acid	Raised gradually over a week to a final amount of 20-70 g/day for 5-36 months	Intestinal lymphangiectasia: absorption of MCT was "virtually complete" with less than 1% of the ingested MCT appearing in feces. Elimination or reduction of edema was reported in all children. Obstructive jaundice: steatorrhea of LCT was gross, but was abolished by replacement of LCT by MCT. About 4% of the octanoic acid and from 7 to 23% of the decanoic acid was not absorbed. Little or no benefit in growth velocity or liver function was reported. Pancreatic insufficiency: MCT diets reduced fecal lipid content, but normal values were not achieved. Little or no benefit in growth velocity or liver function was reported. Abetalipoproteinemia: although MCT treatment improved fecal lipid levels, little or no benefit in growth velocity or liver function was reported. The authors concluded that "MCT diets controlled the steatorrhoea in all four groups of disorders. Analysis of the faecal fatty acid pattern showed that MCT absorption was somewhat impaired where bile or pancreatic lipase was deficient, but was virtually complete in intestinal lymphangiectasia and a-β-lipoproteinaemia where the intraluminar phase of fat digestion was normal. Control of steatorrhoea improved the general well-being of all the children." No adverse effects attributable to MCT treatment were reported.

Table 7. Studies of MCT in Children.					
Reference	**Study Design & Objective**	**Subjects**	**Source and Characteristics of Test Article**	**Dose & Duration**	**Results**
Neal et al. 2009	Prospective, randomized, parallel group study of MCT in treatment of intractable epilepsy in children	145 children (76 boys and 69 girls) aged 2-16 years with intractable epilepsy	MCT not further described	40-45% of energy in-creasing to 60% for 12 months	15 MCT patients and 10 LCT patients withdrew during the first 3 months and 17 MCT patients and 15 LCT patients withdrew after the third month. There were no differences at any time point between children receiving the MCT diet and those receiving LCT in the frequency of seizures. The most common side effects with both diets were constipation, vomiting, and hunger; diarrhea and abdominal pain were reported only infrequently. The only significant differences in adverse effects between the two dietary groups were a higher incidence of vomiting in the LCT group at 12 months and more frequent reports of lack of energy in the LCT group at 3 months. The authors concluded that, "This study has shown classical [LCT-based] and MCT ketogenic diet protocols to be comparable in efficacy and tolerability."

6.5.2.5. Studies in Adults

These studies are discussed below and summarized in Table 8.

In a prospective, randomized, crossover study (Hashim et al. 1960), eight hospitalized patients (health status not reported), 3 men and 5 women aged 42-62 (mean age 52.5±7.4 years), were fed formula diets containing either MCT derived from coconut oil [77.7% octanoic, 19.6% decanoic, 1.9% hexanoic, and 0.8% dodecanoic], butter, or corn oil as the sole isocaloric source of dietary fat, which provided 40% of calories. Half of the patients received corn-oil formula for 4 weeks, then MCT formula for 4 weeks, and corn-oil formula again for 4 weeks; the other half of the patients followed the same design with the butter formula. Blood was sampled every few days and analyzed for TC and phospholipids. The MCT- and corn-oil diets produced significantly reduced levels of TC compared to levels achieved on the butter diet. The authors reported:

> "All of the formula diets were well tolerated except during a period of 3-4 days, characterised by nausea and abdominal fullness, before the subjects became adjusted to the M.C.T. formula. But this transient discomfort did not prevent them from consuming and retaining the formula. Moderate constipation was a common complaint regardless of the fat source. No diarrhea or change in the gross character of the stools was encountered."

In an open-label study (Freund and Weinster 1966) in which 3 insulin-dependent diabetics and 4 apparently healthy subjects ingested a bolus dose of 25 ml MCT, the mean ketogenic response of the diabetic patients was approximately 2.5 times greater than that for the healthy volunteers. After a dose of 30 ml MCT, peak acetone levels of approximately 1.0 mg acetone/100 ml alveolar air were reached at 6 hours. This study showed that the ingestion of MCT results in an increase in acetone production in end-expiratory air; acetone levels were assumed to reflect the ketogenic effect of MCT. Acetone production could be antagonized by the concomitant ingestion of sucrose. The authors suggested that "the magnitude of ketosis in man is the result of carbohydrate deficiency relative to the amount of fat entering the liver."

Keyayoglou et al. (1973) reported on a study involving 10 women aged 43-62 years (mean age 53.4±6.7 years) with primary biliary cirrhosis who were administered 10 mCi $^{47}CaCl_2$ before and after they received 60 ml MCT (23.2% octanoic, 59.4% decanoic, 17.4% dodecanoic acid) for 4 weeks. Total body retention of ^{47}Ca, determined 7 days post-treatment, was significantly higher after MCT treatment than at baseline. The authors concluded that MCT-based diets in patients with primary biliary cirrhosis "restores the defective calcium absorption to normal." They reported that, "One patient with primary biliary cirrhosis developed diarrhoea while receiving the oil but the problem was overcome by giving the oil in frequent small doses. All the other patients . . . tolerated the oil well."

The Cosmetics, Toiletries and Fragrance Association (CTFA 1980) conducted a human study reported by Traul et al. (2000). Four apparently healthy adults were given 1 g MCT/kg bw after an overnight fast. The MCT consisted of 71% octanoic, 25% decanoic, and 3% dodecanoic acid. Analysis of blood taken 4 hours after exposure showed a "high proportion" of octanoic acid

and a "low proportion" of LCFA. Traul et al. (2000) stated that, "No toxicologic symptoms were reported."

In a randomized double-blind crossover study of the relative effects of MCT and LCT on thermogenesis (Hill et al. 1989), 10 apparently healthy men aged 22-44 years were overfed (150% of estimated energy requirement) liquid formula diets containing 40% of calories as fat in the form of either MCT (66% octanoic and 34% decanoic acid) or LCT for one week, followed by the other type of triacylglycerol, MCT or LCT. There was no washout period. While the resting metabolic rate was not affected by either treatment, overfeeding with the MCT diet produced higher fasting serum levels of β-OHB and significantly greater thermogenesis than did LCT feeding. The authors concluded that this increased energy expenditure "provides evidence that excess energy derived from MCT is stored with a lesser efficiency than is excess energy derived from dietary LCT." No adverse effects due to the MCT diet were reported.

In a second published article (Hill et al. 1990), the authors reported on the blood lipid profiles reported in the previously-described study (Hill et al. 1989). Compared to baseline measures, TC was significantly reduced by the LCT diet but not by MCT, but a significant threefold increase in serum TAG was reported after the MCT diet but not with the LCT diet. The serum TAG after MCT feeding included 10% MCT and 40% C16:0, while after LCT feeding the serum TAG included only 1% MCT and 20% C16:0. The authors concluded that these findings indicate that "excess dietary MCT cause a significant increase in the hepatic synthesis of these fatty acids through *de novo* synthesis and/or chain elongation and desaturation."

Gogos et al. (1990) reported the effects of different types of total parenteral nutrition (TPN) on T-lymphocyte subpopulations and NK cells in an open-label study with an uncertain number of "malnourished, seriously ill patients." The written description of the subjects reported the number as 43, 22 suffering from benign diseases and 21 from malignant diseases. Eleven patients received TPN based on glucose only, 16 received TPN with LCT only, and 16 received TPN with a 50:50 mixture of LCT and MCT. In the two TPN regimes that included fat, the fat provided 55% of calories. However, a table of subject characteristics reported the number of patients as 60, 33 with benign disease and 27 with malignant disease, with 20 patients assigned to each TPN type. Both the written and tabular descriptions reported that 15 apparently healthy adults were included as controls and not placed on TPN.

The TPN solutions, designed to be isocaloric, isovolemic, and isonitrogenous, were given through a central venous catheter placed in a subclavian vein. Body weight, serum albumin, serum transferrin, and T-cell subsets (total T cells, helper T cells, suppressor T cells, and NK cells) were measured at baseline and after 10 days of TPN. The seriously ill patients had significantly lower numbers of total T cells and NK cells than did the healthy controls, but the TPN groups did not differ before or after TPN. The group receiving LCT, but not that receiving the LCT/MCT blend, showed significantly decreased counts of helper T cells and increased counts of suppressor T cells, resulting in a significant decrease in the ratio of helper to suppressor T cells. The authors suggested that "partially replacing LCTs with MCTs in TPN formulas may have important advantages for seriously ill patients by providing a valuable energy source," and "may better support host bactericidal capacity than similar regimens that use LCTs

as the sole lipid source." The authors also concluded that, "We must stress . . . that we found no differences in morbidity or mortality among the study groups."

Sedman et al. (1991), reported on a prospective, randomized, double-blind trial that investigated the immunological effects of 3 total parenteral nutrition (TPN) regimens in 33 preoperative patients (18 men and 15 women; mean age = 66 years) with gastrointestinal cancer. Two regimens provided 50% of the calories from either LCT or a 50:50 blend of LCT and MCT (n = 12 each), while the third regimen derived all its calories from glucose (n = 9); all regimens were isocaloric and isonitrogenous. Immunological studies of T-cell function (lymphocyte transformation in response to concanavalin A and IL-2 production) and lymphocytotoxicity (spontaneous NK-cell activity and lymphokine-activated killer [LAK] cell activity) were performed using freshly isolated peripheral blood lymphocytes at baseline and after 7 days of TPN.

After a week of TPN, NK and LAK activity were significantly higher in patients receiving the MCT-LCT blend, while significantly lower LAK activity occurred in patients receiving the LCT-alone solution. IL-2 content in activated T lymphocyte supernatants was significantly elevated from baseline in patients receiving the LCT solution but was unchanged in those receiving the LCT-MCT blend. The authors suggested that TPN with LCT perturbs cytokine interactions by interfering with the binding of IL-2 to its receptor, resulting in immunosuppression, but that replacement of a portion of the LCT with MCT "provides a more appropriate environment for optimal IL-2/NK cell reactions to occur."

In an open-label study reported by Peters et al. (1991), 20 healthy adults (10 of each sex) aged 20-60 years consumed chocolate confections providing 24 g caprenin (a mixed-chain MCT/LCT consisting of 23.2% octanoic, 26.6% decanoic, and 45.0% docosanoic acids) per day for 5 days. Stool samples were tested before and after the intervention and analyzed for C20:0, C22:0, and C24:0 fatty acid content. Based on the level of fat absorption and the heat loss due to metabolism of the medium-chain fatty acids, the authors calculated a caloric value of caprenin of 5 kcal/g. This study was unusual in that it included an extensive discussion of clinical experience:

> "Because caprenin consumption leads to an increase in fecal fat output, it was of interest to collect information about any symptoms that might be related to consumption of the test material. . . . a total of 41 clinical experiences during the 19-day period. . . . About 83% of those experiences recorded were evaluated as slight. Only 3 experiences were considered marked. One female subject reported a migraine headache on day 1 of the study. Two other females reported marked menstrual cramps, one on day 3 and one on day 8. Furthermore, there were an equal number of experiences in both the prewashout (n = 17) and the treatment periods (n = 16). Clinical experiences also were evaluated as they related to body system. . . . a wide variety of symptoms were reported, a pattern that is observed commonly during the conduct of metabolic ward studies. About 37% of the experiences were confined to the gastrointestinal system. These experiences included upset stomach, nausea, constipation/hard stool, diarrhea, and abdominal pain. Once again, this is consistent with the experience of conducting a metabolic ward study. Change in bowel habits is one of the most common symptoms reported in inpatient studies in which activity of the subjects is restricted and they are placed on a fixed diet.

> Because of the type of symptoms reported, the overall low degree of severity, and the equal distribution of experiences across both treatment and nontreatment phases of the study, none of the clinical experiences reported were considered to be related to the consumption of caprenin."

Eckel et al. (1992) reported the effect of MCT on insulin-mediated glucose metabolism in non-insulin-dependent diabetes mellitus (NIDDM) patients in a prospective, randomized, single-blinded crossover study. Ten NIDDM patients aged 40.3±2.0 years, 3 men and 7 women, were enrolled as well as 4 hypertriglyceridemic patients, 2 of each sex, aged 39.8±3.4 years, and 6 apparently healthy controls, 2 men and 4 women, aged 27.7±1.6 years. All study participants consumed either an LCT diet (40% of calories from LCT) or an MCT diet (31% of calories from MCT [not further described] and 9% from LCT) for 4 days and then the alternative diet for 4 days. Urine ketones were measured each morning and blood glucose several times a day; insulin responsiveness was measured on the last day of each diet using a euglycemic clamp. At that time, gluteal adipose tissue, adipose tissue lipoprotein lipase, and blood levels of β-OHB, insulin, free fatty acids, TC, TAG, HDL, carnitine, short-chain acylcarnitines, and long-chain acylcarnitines were also measured.

Diet had no effect on fasting blood glucose concentration, but MCT significantly reduced preprandial excursions (substantial increases or decreases in fasting glucose levels prior to meals) and increased the glucose load needed to maintain euglycemia during insulin infusion. The authors concluded that diets containing MCT "increased insulin-mediated glucose metabolism in both diabetic patients and non-diabetic subjects. In diabetic subjects, this effect appears to be mediated by increases in insulin-mediated glucose disposal." They also concluded that, "Whatever the cellular mechanism, the safety of short-term MCT administration in diabetic patients has been demonstrated, with no significant change in fasting serum β-OHB levels and only minor gastrointestinal side effects that improved with time."

In a prospective, randomized, double-blind, controlled study, Nosaka et al. (2003) reported on the effects of ingestion of margarines based on MCT and LCT. A total of 73 generally healthy adults (55 men and 18 women) aged 19-58 years (mean age 37.6±10.5 years) were enrolled. Individuals with nonobese diabetes, hyperlipidemia, or obesity were not excluded, but none was undergoing treatment. All enrollees consumed a diet providing 65-73 g fat/day for 12 weeks, including 14 g margarine. For half of the participants, the margarine was based on LCT and contained only 0.6% of the fat in the form of fatty acids with C14:0 or less; the other volunteers consumed margarine with the fat including 39.0% octanoic acid and 13.0% decanoic acid. Bodyweight, body composition, subcutaneous and visceral fat, and blood chemistries (insulin, ketones, glucose, TC, TAG, LDL, VLDL, HDL, AST, ALT, and γ-glutamyl transpeptidase) were measured at baseline and at 4, 8, and 12 weeks.

Patients on the MCT diet exhibited significant decreases in bodyweight, BMI, waist circumference, body fat ratio, areas of subcutaneous and visceral fat, VLDL, and HDL as compared to baseline values and those on the LCT diet. The authors concluded that, "our results suggest that the intake of margarine containing 5 g of MCT significantly suppressed body fat, subcutaneous fat and visceral fat accumulation compared with comparable LCT intakes, when

the subjects consumed a strictly controlled diet." No adverse effects and no adverse changes in blood biochemistry were reported in this study.

St-Onge et al. (2003a) enrolled 24 overweight (BMI 25-31 kg/m^2) but otherwise apparently healthy men aged 43.1±2.3 years in a randomized controlled crossover trial of the effects of diets rich in either MCT or LCT. The MCT-rich diet provided 40% of energy from fat, including 67.4% MCT (37.0% octanoic and 30.4% decanoic acids); the LCT-rich diet also had 40% energy from fat, 75% olive oil. Volunteers were randomly assigned to consume each diet for 28 days with a 4-week intervening washout. Bodyweight was measured daily and body composition was measured by magnetic resonance imaging on days 1 and 29 of each phase. Nineteen volunteers also participated in energy-expenditure assessment, including fat and carbohydrate oxidation rates, with a metabolic monitor on days 2 or 3 and 27 or 28. These subjects also provided fecal samples midway through each phase for determination of fecal fat excretion. A separate subgroup of 5 subjects completed satiety questionnaires 0, 2, and 4 hours after consuming breakfast containing either MCT or olive oil and were then served an *ad libitum* meal at which their consumption was measured.

Mean bodyweights decreased significantly during both diet regimens, but upper body adipose tissue decreased significantly more during the MCT phase than the olive-oil phase. No other measures showed significant differences between the diet phases. The authors did not report any adverse effects from the dietary interventions. They concluded that, "consumption of a diet rich in MCT for 28 days improves adiposity, particularly upper body adiposity in overweight men."

In a companion study to their study of the effects of MCT in overweight men (St-Onge et al. 2003a), St-Onge et al. (2003b) studied the effects of MCT in overweight women. Seventeen obese (mean BMI = 31.8±0.9 kg/m^2) but otherwise apparently healthy women aged 44.3±3.8 years participated in a prospective, randomized crossover trial. During each experimental phase, lasting 27 days, participants resided and consumed all meals in a Clinical Nutrition Research Unit. Diets contained 40% of energy from fat; in the LCT diet, 75% of the fat was provided by beef tallow, while in the MCT diet, 67% of the fat was provided by a commercial MCT oil composed of 49% octanoic acid and 50% decanoic acid. Bodyweight was measured daily and body composition and energy expenditure were measured at the beginning and end of each phase.

The diets did not have different effects on total or subcutaneous adipose tissue volumes, but energy expenditure and fat oxidation were significantly higher when consuming the MCT diet. The authors concluded that MCT "may promote long term weight maintenance in obese women." The only report of intolerance was the inability of 2 women to tolerate the LCT diet; no intolerance or side effects from the MCT diet were reported. The authors did not discuss the difference, if any, between the effects of MCT on women in this study and its effects on men in St-Onge et al. (2003a), but the results of the two studies appear to be similar.

St-Onge et al. (2003c) enrolled 30 apparently healthy men aged 26-61 years in a prospective, randomized crossover study of the effects of a combination of MCT, phytosterols, and flaxseed oil on blood lipid concentrations and LDL particle size. The experimental oil had

36.95% octanoic and 30.35% decanoic acid as well as 13.81% oleic acid; the control was olive oil, with 71% oleic acid. Fat provided 40% of the calories in both diets, with the experimental or control oil providing 75% of the fat. Men were randomly assigned to consume one of the diets for 29 days and the other diet for a further 29 days after a 4-week washout period. Body composition and energy expenditure were measured at the beginning and end of each diet periods and blood was collected in the morning on days 1, 28, and 29 of each period for analysis of TAG, TC, HDL, and LDL peak particle density.

Six subjects withdrew from the study for reasons not related to the dietary interventions. TC and LDL both decreased significantly more in men consuming the MCT diet than when they consumed the control diet, and peak LDL particle size was significantly greater. The authors concluded that "those who consume a diet containing [MCT, phytosterols, and flaxseed oil] have a better lipid profile than those who consume a diet rich in olive oil." No adverse effects of the blend of MCT, phytosterols, and flaxseed oil were reported.

Han et al. (2007) reported on the effects of MCT on moderately overweight adults with type 2 diabetes mellitus. Forty subjects (8 men, 32 women) aged 45-65 years, weighing 60.8±11.1 kg, and having type 2 diabetes mellitus for 5-10 years standing but otherwise apparently healthy were randomly assigned to receive a diet containing 18 g/day of either MCT (not further described) or LCT (corn oil) for 90 days. Bodyweight, waist circumference, and fasting blood parameters (glucose, insulin, TAG, TC, HDL, apolipoproteins A and B, and C-peptide concentration) were measured on days 0, 45, and 90; LDL and insulin sensitivity were calculated.

All participants completed the study. The MCT group, but not the LCT group, showed significant reductions in body weight, waist circumference, TC, and insulin resistance and a significant increase in serum C-peptide. The authors concluded that, "Our results suggest that this group of subjects [i.e., moderately overweight, middle-aged, type 2 diabetics) could benefit from long-term consumption of a moderate dose of MCT in a free-living environment." The authors reported that, "A few subjects [neither number nor group membership given] reported slight stomach ache and diarrhea on the first 1 or 2 days, but the symptoms disappeared thereafter." No other adverse effects of either intervention were reported.

To investigate the effects of MCT on weight loss and metabolic cardiovascular risk, 31 overweight but otherwise apparently healthy men (n = 3) and women (n = 28) aged 19-50 years (mean age = 37.0±2.1 years) participated in a prospective, randomized 16-week weight-loss program with lipids provided by either MCT or olive oil (St-Onge and Bosarge 2008). The MCT oil contained 55.0% octanoic and 45.0% decanoic acids; the olive oil, chosen for its high content of monounsaturated fatty acids, contained 71.3% oleic, 11.3% palmitic, and 9.8% linoleic acid. Men's diets included 24 g/day of one of the oils while women's diets included 18 g—both approximately 12% of their daily caloric intake. Bodyweight and waist circumference were measured weekly while blood pressure was measured and fasting blood was taken at 0, 8, and 16 weeks for analysis of TC, LDL, HDL, TAG, insulin, and glucose. Adipose tissue distribution was assessed at 0 and 16 weeks.

Patients consuming MCT oil lost significantly more weight than did those on the olive-oil diet and completed the study with significantly lower total fat mass, trunk-fat mass, and intraabdominal adipose tissue. No adverse effects were reported, and the authors concluded that "MCT oil can be successfully used in a weight-management program to enhance weight loss."

In a companion article describing other findings from the same study, particularly those indicative of cardiovascular disease risk, St-Onge et al. (2008) reported that the diets did not have significantly different effects on blood pressure or any of the tested metabolic parameters. No adverse effects were reported and no patient in the MCT group developed metabolic syndrome during the study; one olive-oil-group patient developed metabolic syndrome. The authors concluded that, "MCT oil consumption, at a level of approximately 18–24 g/d, does not have detrimental effects on cardiovascular disease risk factors."

In a prospective open-label study, 46 hospitalized patients with several conditions (most often gastrointestinal dysfunction [n = 21] or lymphatic anomalies [n = 15], along with dyslipidemia [n = 5], exocrine pancreatic insufficiency [n = 4], and epilepsy [n = 1]) were placed on MCT therapy in which MCT were used as fats in enteral solutions and as cooking oils (Li et al. 2015). MCT levels were not reported, nor were patient characteristics. MCTs were presented either enterally or in the diet, but the numbers and conditions of patients in each group were not reported. Improvement was reported in 71% of the patients with gastrointestinal dysfunction and about 50% of the remaining patients; no adverse effects from MCT administration were reported for any of the treated patients.

Qiu et al. (2017) reported on a prospective, randomized, single-blind, controlled, multicenter trial of the use of MCT in enteral formula to improve feeding tolerance in critically ill patients. A total of 144 patients between the ages of 18 and 85 (110 men and 34 women; mean age = 65.2±18.3 years) admitted to intensive care units in 7 Chinese hospitals, all requiring enteral nutrition for at least 5 days, was enrolled; 71 patients were randomly assigned to receive enteral formula with 20% of the lipid as MCT while 73 received standard enteral formula containing no MCT. The fatty-acid content of the MCT was not described. Patients were assessed for formula intake, signs of feeding intolerance (Diarrhea, vomiting, gastric retention, or abdominal distension), and health outcomes (ventilator-free days, length of stay in the ICU and in the hospital, and mortality).

There were no differences in health outcomes between the feeding groups. The patients receiving the MCT enteral formula had significantly greater intake of protein and calories than did the control patients and significantly less intolerance to the formula. The total incidence of feeding intolerance was 42.3% and 65.7% in the MCT and control groups, respectively. On each day of days 1-5, the incidence of feeding intolerance in the MCT and control groups, respectively, were: Day 1—11.3 and 31.5%; Day 2—18.3 and 32.9%; Day 3—14.1 and 34.2%; Day 4—25.4 and 34.2%; Day 5—26.1 and 30.4%. The authors stated that, "To our knowledge, this study is the first large randomized controlled trial that indicated that a fat-modified formula could alleviate feeding intolerance in critically ill patients."

Table 8. Studies of MCT in Adults.					
Reference	**Study Design & Objective**	**Subjects**	**Source and Characteristics of Test Article**	**Dose & Duration**	**Results**
CTFA 1980 Reported by Traul et al. 2000	Single-dose study of MCFA absorption from MCT	4 apparently healthy adults	MCT with 71% octanoic, 25% decanoic, and 3% dodecanoic acid	1 g/kg bw as a bolus dose	Analysis of blood taken 4 hours after exposure showed a "high proportion" of octanoic acid and a "low proportion" of LCFA. Traul et al. (2000) stated that, "No toxicologic symptoms were reported."
Eckel et al. 1992	prospective, randomized, single-blinded crossover study of the effect of MCT on insulin-mediated glucose metabolism in NIDDM patients	10 NIDDM patients (3 men and 7 women) aged 40.3±2.0 years, and 4 hypertriglyceridemic patients (2 of each sex) aged 39.8±3.4 years, and 6 healthy controls (2 men and 4 women) aged 27.7±1.6 years	MCT not further described	31% of calories for 4 days	Diet had no effect on fasting blood glucose concentration, but MCT reduced preprandial excursions (substantial increases or decreases in fasting glucose levels prior to meals) and increased the glucose load needed to maintain euglycemia during insulin infusion. The authors concluded that diets containing MCT "increased insulin-mediated glucose metabolism in both diabetic patients and non-diabetic subjects. In diabetic subjects, this effect appears to be mediated by increases in insulin-mediated glucose disposal." They also concluded that, "Whatever the cellular mechanism, the safety of short-term MCT administration in diabetic patients has been demonstrated, with no significant change in fasting serum p-OHB levels and only minor gastrointestinal side effects that improved with time."

Table 8. Studies of MCT in Adults.					
Reference	**Study Design & Objective**	**Subjects**	**Source and Characteristics of Test Article**	**Dose & Duration**	**Results**
Freund and Weinster 1966	Open-label study of ketogenic effect of MCT	3 insulin-dependent diabetics and 4 apparently healthy subjects	MCT not further described	25 or 30 ml as a bolus dose	After a bolus dose of 25 ml of MCT, the mean ketogenic response of the diabetic patients was approximately 2.5 times greater than that of the healthy volunteers. After a dose of 30 ml MCT, peak acetone levels of 1.0 mg acetone/100 ml alveolar air were reached at 6 hours. This study showed that the ingestion of MCT results in an increase in acetone production in end-expiratory air, reflecting the ketogenic effect of MCT. The authors suggested that "the magnitude of ketosis in man is the result of carbohydrate deficiency relative to the amount of fat entering the liver."
Gogos et al. 1990	Open-label study of the effects of MCT in TPN on T-lymphocyte subpopulations and NK cells in malnourished, seriously ill patients	43 adults, 22 suffering from benign diseases and 21 from malignant diseases or 60 adults, 33 suffering from benign and 27 from malig-nant diseases	MCT, not further described, in a 1:1 mixture with LCT in TPN formula	Neither dose nor duration were reported	The group receiving LCT, but not that receiving the LCT/MCT blend, showed decreased counts of helper T cells and increased counts of suppressor T cells, resulting in a significant decrease in the ratio of helper to suppressor T cells. The authors suggested that "partially replacing LCTs with MCTs in TPN formulas may have important advantages for seriously ill patients by providing a valuable energy source," and "may better support host bactericidal capacity than similar regimens that use LCTs as the sole lipid source." The authors also concluded that, "We found no differences in morbidity or mortality among the study groups."

Table 8. Studies of MCT in Adults.					
Reference	**Study Design & Objective**	**Subjects**	**Source and Characteristics of Test Article**	**Dose & Duration**	**Results**
Han et al. 2007	Prospective, randomized study of the effects of MCT on moderately overweight adults with NIDDM	40 patients (8 men and 32 women) aged 45-65 years, weighing 60.8±11.1 kg, and having NIDDM for 5-10 years	MCT not further described	18 g/day for 90 days	All participants completed the study. The MCT group showed reductions in body weight, waist circumference, TC, and insulin resistance and an increase in serum C-peptide. The authors concluded that, ". . . this group of subjects [i.e., moderately overweight, middle-aged, type 2 diabetics) could benefit from long-term consumption of moderate dose of MCT in a free-living environment." The authors reported that, "A few subjects [neither number nor group membership given] reported slight stomachache and diarrhea on the first 1 or 2 days, but the symptoms disappeared thereafter." No other adverse effects of either intervention were reported.
Hashim et al. 1960	prospective, randomized, crossover study	8 hospitalized patients, 3 men and 5 women (health status not reported) aged 42-62 years (mean age 52.5±7.4 years)	MCT derived from coconut oil (1.9% hexanoic, 77.7% octanoic, 19.6% decanoic, and 0.8% do-decanoic acid)	4 weeks	The MCT diet produced reduced levels of TC. The authors reported: "All of the formula diets were well tolerated except during a period of 3-4 days, characterised by nausea and abdominal fullness, before the subjects became adjusted to the M.C.T. formula. But this transient discomfort did not prevent them from consuming and retaining the formula. Moderate constipation was a common complaint regardless of the fat source. No diarrhea or change in the gross character of the stools was encountered."

Table 8. Studies of MCT in Adults.					
Reference	**Study Design & Objective**	**Subjects**	**Source and Characteristics of Test Article**	**Dose & Duration**	**Results**
Hill et al. 1989 Hill et al. 1990	Prospective randomized double-blind crossover study of the relative effects of MCT and LCT on thermogenesis	10 apparently healthy men aged 22-44 years	MCT with 66% octanoic and 34% decanoic acid	40% of lipid for 1 week	Compared to baseline measures, TC was reduced by the LCT diet but not by MCT, but a threefold increase in serum TAG was observed after the MCT diet but not with the LCT diet. The serum TAG after MCT feeding included 10% MCT and 40% C16:0, while after LCT feeding the serum TAG included only 1% MCT and 20% C16:0. While the resting metabolic rate was not affected by either treatment, overfeeding with the MCT diet produced higher fasting serum levels of β-OHB and greater thermogenesis than did LCT feeding. The authors concluded that this increased energy expenditure "provides evidence that excess energy derived from MCT is stored with a lesser efficiency than is excess energy derived from dietary LCT." No adverse effects due to the MCT diet were reported.
Keyayoglou et al. 1973	Open-label study of the effect of MCT on Ca absorption in patients with primary biliary cirrhosis	10 women aged 43-62 years (mean age 53.4±6.7 years) with primary biliary cirrhosis	MCT with 23.2% octanoic, 59.4% decanoic, 17.4% dodecanoic acid	60 ml	Total body retention of Ca was significantly higher after MCT treatment than at baseline. The authors concluded that MCT-based diets in patients with primary biliary cirrhosis "restores the defective calcium absorption to normal." They reported that, "One patient with primary biliary cirrhosis developed diarrhoea while receiving the oil but the problem was overcome by giving the oil in frequent small doses. All the other patients . . . tolerated the oil well."

Table 8. Studies of MCT in Adults.					
Reference	**Study Design & Objective**	**Subjects**	**Source and Characteristics of Test Article**	**Dose & Duration**	**Results**
Li et al. 2015	Open-label study	46 patients with GI dysfunction, lymphatic anomalies, dyslipidemia, exocrine pancreatic insufficiency, or epilepsy	MCT not further described	Dose and duration were not reported	Improvement was reported in 71% of the patients with gastrointestinal dysfunction and about 50% of the remaining patients; no adverse effects from MCT administration were reported for any of the treated patients.
Nosaka et al. 2003	Prospective, randomized, double-blind, controlled study of MCT in obesity	73 generally healthy adults (55 men and 18 women) aged 19-58 years (mean age 37.6±10.5 years)	MCT with 75% octanoic and 25% decanoic acid	7.3 g/day for 12 weeks	Patients on the MCT diet exhibited significant decreases in bodyweight, BMI, waist circumference, body fat ratio, areas of subcutaneous and visceral fat, VLDL, and HDL as compared to baseline values and those on the LCT diet. The authors concluded that, "our results suggest that the intake of margarine containing 5 g of MCT significantly suppressed body fat, subcutaneous fat and visceral fat accumulation compared with comparable LCT intakes, when the subjects consumed a strictly controlled diet." No adverse effects were reported in this study and no adverse changes in blood biochemistry were reported.

Table 8. Studies of MCT in Adults.					
Reference	**Study Design & Objective**	**Subjects**	**Source and Characteristics of Test Article**	**Dose & Duration**	**Results**
Peters et al. 1991	Open-label study of the caloric value of caprenin	20 healthy adults (10 of each sex) aged 20-60 years	Caprenin (a mixed-chain MCT/LCT with 23.2% octanoic, 26.6% decanoic, 45.0% doco-sanoic acids)	24 g/day for 5 days	The authors calculated a caloric value of caprenin of 5 kcal/g. There were 41 clinical experiences during the 19-day period; 83% were slight and 3 were marked. 1 female reported a migraine headache on day 1 of the study. 2 females reported marked menstrual cramps. There were an equal number of experiences in the prewashout and treatment periods. A wide variety of symptoms were reported,. 37% confined to the GI system including upset stomach, nausea, constipation/ hard stool, diarrhea, and abdominal pain. None of the clinical experiences reported were considered to be related to the consumption of caprenin.
Qiu et al. 2017	Prospective, randomized, single-blind, controlled, multicenter trial of MCT in enteral formula to improve feeding tolerance in critically ill patients	144 patients (110 men and 34 women) between the ages of 18 and 85 (mean age = 65.2±18.3 years)		20% of the lipid	There were no differences in health outcomes between the feeding groups. The patients receiving the MCT enteral formula had significantly less intolerance to the formula. The total incidence of feeding intolerance was 42.3% and 65.7% in the MCT and control groups, respectively. On each day of days 1-5, the incidence of feeding intolerance in the MCT and control groups, respectively, were: Day 1—11.3 and 31.5%; Day 2—18.3 and 32.9%; Day 3—14.1 and 34.2%; Day 4—25.4 and 34.2%; Day 5—26.1 and 30.4%.

Table 8. Studies of MCT in Adults.					
Reference	**Study Design & Objective**	**Subjects**	**Source and Characteristics of Test Article**	**Dose & Duration**	**Results**
Sedman et al. 1991	Prospective, randomized, double-blind trial, of the immune-logical effects of MCT in total par-enteral nutrition	33 pre-operative patients (18 men and 15 women; mean age = 66 years) with gastro-intestinal cancer	MCT not further described in a 50:50 blend with LCT	50% of the lipid for 7 days	After a week of TPN, NK and lymphokine-activated killer [LAK] cell activity were higher in patients receiving the MCT/LCT solution, while lower LAK activity occurred in patients receiving the LCT solution. IL-2 content in activated T lymphocyte supernatants was elevated from baseline in patients receiving the LCT solution but was unchanged in those receiving the LCT/MCT blend. The authors suggested that TPN with LCT perturbs cytokine interactions by interfering with the binding of IL-2 to its receptor, resulting in immunosuppression, but that replacement of a portion of the LCT with MCT "provides a more appropriate environment for optimal IL-2/NK cell reactions to occur."
St-Onge et al. 2003a	Prospective randomized controlled crossover trial of the weight-loss effects of diets rich in MCT on men	24 overweight (BMI 25-31 kg/m^2) but otherwise apparently healthy men aged 43.1±2.3 years	MCT with 37.0% octanoic and 30.4% decanoic acid	27% of energy for 28 days	Mean bodyweights decreased significantly during both diet regimens, but upper body adipose tissue decreased more during the MCT phase than the olive-oil phase. No other measures showed significant differences between the diet phases. The authors did not report any adverse effects from the dietary interventions.
St-Onge et al. 2003b	Prospective randomized controlled crossover trial of the weight-loss effects of diets rich in MCT on women	17 obese (mean BMI = 31.8±0.9 kg/m^2) but otherwise apparently healthy women aged 44.3±3.8 years	MCT with 49% octanoic and 50% decanoic acid	27% of energy for 27 days	The diets did not have different effects on total or subcutaneous adipose tissue volumes, but energy expenditure and fat oxidation were higher when consuming the MCT diet. The authors concluded that MCT "may promote long term weight maintenance in obese women." The only report of intolerance was the inability of 2 women to tolerate the LCT diet; no intolerance or side effects from the MCT diet were reported.

Table 8. Studies of MCT in Adults.					
Reference	**Study Design & Objective**	**Subjects**	**Source and Characteristics of Test Article**	**Dose & Duration**	**Results**
St-Onge et al. 2003c	Prospective, randomized crossover study of the effects of MCT, phyto-sterols, and flaxseed oil on blood lipid con-centrations and LDL particle size	30 apparently healthy men aged 26-61 years	MCT with 36.95% octanoic and 30.35% decanoic acid as well as 13.81% oleic acid	30% of energy for 29 days	Six subjects withdrew from the study for reasons not related to the dietary interventions. TC and LDL both decreased more in men consuming the MCT diet than when they consumed the control diet, and peak LDL particle size was greater. The authors concluded that "those who consume a diet containing [MCT, phytosterols, and flaxseed oil] have a better lipid profile than those who consume a diet rich in olive oil." No adverse effects of the blend of MCT, phytosterols, and flaxseed oil were reported.
St-Onge and Bosarge 2008 St-Onge et al. 2008	Prospective, randomized, controlled test of the effects of MCT on weight loss and metabolic cardiovascular risk	31 overweight but otherwise apparently healthy men (n = 3) and women (n = 28) aged 19-50 years (mean age = 37.0±2.1 years)	MCT with 55.0% octanoic and 45.0% decanoic acid	24 g/day (men) or 18 g/day (women) for 16 weeks	Patients consuming MCT oil lost more weight than did those on the olive-oil diet and completed the study with lower total fat mass, trunk-fat mass, and intraabdominal adipose tissue. The diets did not have significantly different effects on blood pressure or any of the tested metabolic parameters. No patient in the MCT group developed metabolic syndrome during the study and no adverse effects were reported, and the authors concluded that "MCT oil consumption, at a level of approximately 18–24 g/d, does not have detrimental effects on cardiovascular disease risk factors."

6.6. Reviews and Meta-Analyses

Assessing medical and nutritional uses of MCT, Bach and Babayan (1982) reviewed more than a hundred *in vitro*, animal, and human research studies available at that time, including the physicochemical properties of MCT. They reported that the melting points of MCFA are substantially lower than those of LCFA (e.g., 16.7°C for octanoic acid and 31.3°C for decanoic acid as compared with 63.1°C for hexadecanoic [palmitic] acid and 69.3°C for octadecanoic [stearic] acid) and that, by virtue of their smaller molecular size, MCFA are relatively soluble in water. The smaller size of MCT allows them to hydrolyze more quickly, even in a state of deficiency of bile salts or pancreatic lipase, and to be absorbed as triacylglycerols.

Bach and Babayan (1982) reported that MCFA follow the portal venous system rather than the lymphatic system as do LCFA, and reach the liver more rapidly and more abundantly. Unlike LCFA, MCFA are not significantly incorporated into the lipids synthesized by the hepatic tissue. Rather, they cross the mitochondrial membrane and are acylated by octanoyl-CoA synthetase, after which they are rapidly oxidized, resulting in an excess of acetyl-CoA, which leads to the synthesis of ketone bodies—a process little affected by simultaneous ingestion of carbohydrates such as glucose and fructose.

Because of its ease of absorption, MCT have been used to treat maldigestion and malabsorption of LCT (Bach and Babayan 1982). Since they provide a rapid source of energy, MCT have been included in the nutritional management of severely undernourished patients and children during normal or retarded growth. Bach and Babayan (1982) reviewed the limited literature available at the time regarding the use of MCT in controlling obesity, concluding that it was not yet well understood despite some encouraging studies in animals. The also reviewed contraindications for the use of MCT, including diabetes, metabolic acidosis, and cirrhosis. The authors provided the following conclusion:

> "The beneficial effects of MCTs are: 1) MCTs are digested, absorbed, and transported easily and rapidly in disorders where the digestion, absorption, or transport of LCTs are not optimal. 2) MCTs are oxidized rapidly in the organism and they have a very low tendency to deposit as body fat. 3) MCTs are a source of abundant and rapidly available energy. 4) MCTs are ketogenic. 5) MCTs are donors of hydrogen ions and precursors of acetyl-CoA" (Bach and Babayan 1982).

Traul et al. (2000) reviewed the toxicologic properties of MCT and concluded that "MCTs are essentially non-toxic in acute toxicity tests conducted in several species of animals ... exhibit virtually no potential as ocular or dermal irritants ... exhibit no capacity for induction of hypersensitivity ... did not result in notable toxicity [in 90-day studies] whether administered in the diet or by intramuscular injection ... no evidence that intravenous or dietary administration adversely affected reproductive performance or resulted in maternal toxicity, foetal toxicity or teratogenic effects ... do not have the potential to be carcinogenic or mutagenic."

The authors noted that, "It has been established that consumption of MCTs can lead to ketone production, but it is generally accepted that there is no risk of ketoacidosis or ketonaemia with MCTs at levels associated with normal consumption levels." After reviewing a number of human studies—most often in infants—of the effect of MCT on mineral absorption, Traul et al. (2000) concluded that, "Clinical trials have indicated that normal dietary levels of MCTs have no adverse effect on the absorption and retention of calcium, magnesium or phosphorus." After observing that, "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," and that, "humans receiving MCTs parenterally have tolerated doses of 3.0-9.0 g/kg body weight/day for periods of several months without adverse effects, the authors concluded:

> "MCTs exhibit very low levels of toxicity in a variety of laboratory animals and in humans when administered orally, parenterally or by the dermal route. There is no evidence that MCTs are sensitizers and they show little evidence that they are ocular or dermal irritants. 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" (Traul et al. 2000).

In a Cochrane Collaboration review of the effects of different levels of MCT in infant formula in promoting short-term growth of preterm infants, Nehra et al. (2003) evaluated 8 randomized trials enrolling 182 preterm infants. The mean gestational weights of infants in the studies ranged from 29 to 32 weeks and their mean birth weights were between 1010 and 1476 g. Six of the 8 trials compared 2 formulas with low (0-14% of the lipid) or high (38-50% of the lipid) MCT concentrations. One study compared 3 formulas with <10%, 40%, and 80% MCT and one study compared 4 formula with 5%, 17%, 30%, and 43% MCT. All of the studies were short-term with durations of 1-2 weeks.

Meta-analyses of gains in weight, length, and head circumference all indicated no effect on any of these measures of growth. No consistent differences were reported in stool transit time, fecal output, or occurrence of necrotizing enterocolitis. Only 2 studies reported data regarding GI tolerance; one study found significantly more frequent intolerance symptoms (abdominal distension, loose stools, vomiting) among infants consuming formulas with 40% or 80% MCT than those receiving <10% MCT formula, but the other study reported little evidence of intolerance and differences among infants receiving formulas containing 5%, 17%, 30%, or 43% MCT. The Cochrane review authors concluded that, "There is no evidence of difference between high and low MCT formula on short-term growth, gastrointestinal intolerance, or NEC incidence."

6.7. GRAS Determination

6.7.1. Introduction

This section presents an assessment that demonstrates that MCT is safe, and is also GRAS under the Federal Food, Drug, and Cosmetic Act (FFDCA) for addition to exempt infant formulas. This safety assessment and GRAS determination entail two steps. In step one, the safety of the intended use of MCT is demonstrated. In the second step, the intended use of MCT

is determined to be GRAS by demonstrating that its safety is based on generally available information and generally recognized among qualified scientific experts.

The regulatory framework for establishing whether a substance is GRAS in accordance with Section 201(s) of the FFDCA is set forth under 21 CFR §170.30. This regulation states that general recognition of safety may be based on the view of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food. A GRAS determination may be made either: 1) through scientific procedures under 21 CFR §170.30(b); or 2) through experience based on common use in food, in the case of a substance used in food prior to January 1, 1958, under 21 CFR §170.30(c). This GRAS determination employs scientific procedures established under 21 CFR §170.30(b).

In addition to requiring scientific evidence of safety, a GRAS determination also requires that this scientific evidence of safety be generally known and accepted among qualified scientific experts. This "common knowledge" element of a GRAS determination consists of two components: 1) the data and information relied upon to establish the scientific element of safety must be generally available; and 2) there must be a basis to conclude that there is a consensus among qualified experts about the safety of the substance for its intended use.

The criteria outlined above for a scientific procedures GRAS determination are applied below in an analysis of whether MCT is safe and GRAS for the uses and at the use level intended.

6.7.2. Safety of the Intended Use of MCT

A scientific procedures GRAS determination requires first that information about the material establish that the intended use of the material is safe. The FDA has defined "safe" or "safety" for food additives under 21 CFR §170.3(i) as "a reasonable certainty in the minds of competent scientists that the substance is not harmful under its intended conditions of use." This same regulation specifies that three factors must be considered in determining safety. These three factors are:

1) The probable consumption of the substance and of any substance formed in or on food because of its use;

2) The cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet; and

3) Safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of food and food ingredients, are generally recognized as appropriate.

An estimated daily intake (EDI) for the material is derived based on the probable human consumption of the material, taking into account any existing sources of consumption of the material. Finally, the EDI for a substance is compared against a level of consumption that has been shown to be reasonably certain to be without harm. If the EDI is less than or approximates this level, the substance can be considered safe for its intended use (FDA 1993).

The primary fatty acids in MCT are octanoic acid (C8:0), also known as caprylic acid, and decanoic acid (C10:0), also known as capric acid. These fatty acids—as well as the glycerol backbone—have long been a part of the normal food supply, Glycerol occurs in all naturally occurring lipids in the diet, which are invariably in the form of triacylglycerol, and octanoic and decanoic acid are found in most lipids; they are found in the highest concentration, up to about 14%, in coconut and palm kernel oils. It is estimated that these fatty acids account for about 2% of fatty-acid intake in the U.S. diet, which indicates a mean intake of about 2.4 g MCT/day and a 90th percentile intake of about 4.8 g/day of MCT.

Metabolic studies indicate that the smaller molecular weight of medium chain fatty acids allows them to be absorbed more easily and more quickly than are long chain fatty acids, and they follow the portal venous system. They are rapidly oxidized, and little, if any, is stored in adipose tissues. Numerous toxicity studies have found little evidence of toxicity in experimental animals, and extensive research in which MCT has been consumed by human infants, children, and adults—including both healthy and severely compromised individuals—confirms that MCT is safe. Although MCT is ketogenic and ketoacidosis or ketonemia would be severe adverse effects, it is clear that these states cannot be achieved at normal consumption levels of MCT. No other effects of MCT can be considered as potentially adverse.

MCT is intended to be added to exempt infant formulas, including those for infants with cow's milk protein allergy and/or fat malabsorption issues. The concentration levels of MCT in formula ranges with up to 50% of the fat as MCT range from 17 to 20.3 g MCT/1000 ml formula as prepared. The estimated daily intake of MCT from its intended use may be as high as 22 g MCT for infants, including 1.5 g MCT from naturally occurring sources.

It may be concluded that MCT is safe under its intended conditions of use because the intake of MCT resulting from its intended use is within levels shown by animal and human studies of MCT and other oligosaccharides to be tolerable and safe.

6.7.3. General Recognition of the Safety of the Intended Use of MCT

The intended use of MCT has been determined to be safe through scientific procedures set forth under 21 CFR §170.30(b). A comprehensive search of the literature through December 2020 served as the basis for preparation of a monograph summarizing the information available germane to determining the safety of the intended use of MCT in exempt infant formulas. Furthermore, because this safety assessment satisfies the common knowledge requirement of a GRAS determination, this intended use can be considered GRAS.

Determination of the safety and GRAS status of MCT for addition to exempt infant formulas for infants with cow's milk protein allergy, other food allergies, and/or fat malabsorption up to 21 g/1000 ml has been made through the deliberations of a GRAS Panel comprising Joseph F. Borzelleca, Ph.D., James T. Heimbach, Ph.D., and Robert J. Nicolosi, Ph.D. These individuals are qualified by scientific training and experience to evaluate the safety of food and food ingredients. These experts have carefully reviewed and evaluated the publicly available information summarized in this document, and have concluded:

Ingestion of medium chain triacylglycerol from the intended use results in intakes that remain within safe limits established by published animal and human studies. Medium chain triacylglycerol has been sufficiently characterized to ensure that it is a food-grade product. No evidence exists in the available information on medium chain triacylglycerol that demonstrates, or suggests reasonable grounds to suspect, a hazard when medium chain triacylglycerol is added to exempt infant formulas at a level not exceeding 21 g/1000 ml.

It is their opinion that other qualified and competent scientists reviewing the same publicly available data would reach a similar scientific conclusion regarding safety. Therefore, based on scientific procedures, MCT is safe and is GRAS for its proposed use as a fat and energy source for addition to exempt infant formulas at levels not exceeding 21 g/1000 ml.

6.8. Statement Regarding Information Inconsistent with GRAS

I have reviewed the available data and information and am not aware of any data or information that are, or may appear to be, inconsistent with our conclusion of the GRAS status of the intended use of medium-chain triacylglycerol.

7. SUPPORTING DATA AND INFORMATION

7.1. Generally Available Information

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

GENERALLY RECOGNIZED AS SAFE *(GRAS)* NOTICE (Subpart E of Part 170)

Form Approved: OMB No. 0910-0342; Expiration Date: 07/31/2022
(See last page for OMB Statement)

FDA USE ONLY

GRN NUMBER	DATE OF RECEIPT
001049	11/30/2021
ESTIMATED DAILY INTAKE	INTENDED USE FOR INTERNET
NAME FOR INTERNET	
KEYWORDS	

Transmit completed form and attachments electronically via the Electronic Submission Gateway *(see Instructions)*; OR Transmit completed form and attachments in paper format or on physical media to: Office of Food Additive Safety *(HFS-200)*, Center for Food Safety and Applied Nutrition, Food and Drug Administration,5001 Campus Drive, College Park, MD 20740-3835.

SECTION A – INTRODUCTORY INFORMATION ABOUT THE SUBMISSION

1. Type of Submission *(Check one)*

☒ New ☐ Amendment to GRN No. _____ ☐ Supplement to GRN No. _____

2. ☒ All electronic files included in this submission have been checked and found to be virus free. *(Check box to verify)*

3 Most recent presubmission meeting *(if any)* with FDA on the subject substance *(yyyy/mm/dd):* _____

4 For Amendments or Supplements: Is your amendment or supplement submitted in response to a communication from FDA? *(Check one)* ☐ Yes ☐ No If yes, enter the date of communication *(yyyy/mm/dd):* _____

SECTION B – INFORMATION ABOUT THE NOTIFIER

1a. Notifier

Name of Contact Person	Position or Title
Cheryl Callan	Senior Director of Regulatory Affairs

Organization *(if applicable)*: Nestle Nutrition

Mailing Address *(number and street)*: 1812 North Moore Street

City	State or Province	Zip Code/Postal Code	Country
Arlington	Virginia	22535	United States of America

Telephone Number	Fax Number	E-Mail Address
8047425543		cheryl.callan@us.nestle.com

1b. Agent or Attorney *(if applicable)*

Name of Contact Person	Position or Title
James Heimbach	President

Organization *(if applicable)*: JHeimbach LLC

Mailing Address *(number and street)*: 923 Water Street #66

City	State or Province	Zip Code/Postal Code	Country
Port Royal	Virginia	22535	United States of America

Telephone Number	Fax Number	E-Mail Address
8047425543		JH@JHEIMBACH.COM

SECTION C – GENERAL ADMINISTRATIVE INFORMATION

1. Name of notified substance, using an appropriately descriptive term

Medium Chain Triacylglycerol

2. Submission Format: *(Check appropriate box(es))*

☒ Electronic Submission Gateway

☐ Electronic files on physical media

☐ Paper

If applicable give number and type of physical media

_____

3. For paper submissions only:

Number of volumes _____

Total number of pages _____

4. Does this submission incorporate any information in CFSAN's files? *(Check one)*

☐ Yes *(Proceed to Item 5)* ☒ No *(Proceed to Item 6)*

5. The submission incorporates information from a previous submission to FDA as indicated below *(Check all that apply)*

☐ a) GRAS Notice No. GRN _____

☐ b) GRAS Affirmation Petition No. GRP _____

☐ c) Food Additive Petition No. FAP _____

☐ d) Food Master File No. FMF _____

☐ e) Other or Additional *(describe or enter information as above)* _____

6. Statutory basis for conclusions of GRAS status *(Check one)*

☒ Scientific procedures *(21 CFR 170.30(a) and (b))* ☐ Experience based on common use in food *(21 CFR 170.30(a) and (c))*

7. Does the submission (including information that you are incorporating) contain information that you view as trade secret or as confidential commercial or financial information? (see 21 CFR 170.225(c)(8))

☐ Yes *(Proceed to Item 8*

☒ No *(Proceed to Section D)*

8. Have you designated information in your submission that you view as trade secret or as confidential commercial or financial information *(Check all that apply)*

☐ Yes, information is designated at the place where it occurs in the submission

☐ No

9. Have you attached a redacted copy of some or all of the submission? *(Check one)*

☐ Yes, a redacted copy of the complete submission

☐ Yes, a redacted copy of part(s) of the submission

☐ No

SECTION D – INTENDED USE

1. Describe the intended conditions of use of the notified substance, including the foods in which the substance will be used, the levels of use in such foods, and the purposes for which the substance will be used, including, when appropriate, a description of a subpopulation expected to consume the notified substance.

Exempt Infant Formula

2. Does the intended use of the notified substance include any use in product(s) subject to regulation by the Food Safety and Inspection Service (FSIS) of the U.S. Department of Agriculture?

(Check one)

☐ Yes ☒ No

3. If your submission contains trade secrets, do you authorize FDA to provide this information to the Food Safety and Inspection Service of the U.S. Department of Agriculture?

(Check one)

☐ Yes ☐ No , you ask us to exclude trade secrets from the information FDA will send to FSIS.

SECTION E – PARTS 2 -7 OF YOUR GRAS NOTICE

(check list to help ensure your submission is complete – PART 1 is addressed in other sections of this form)

☒ PART 2 of a GRAS notice: Identity, method of manufacture, specifications, and physical or technical effect (170.230).

☒ PART 3 of a GRAS notice: Dietary exposure (170.235).

☒ PART 4 of a GRAS notice: Self-limiting levels of use (170.240).

☒ PART 5 of a GRAS notice: Experience based on common use in foods before 1958 (170.245).

☒ PART 6 of a GRAS notice: Narrative (170.250).

☒ PART 7 of a GRAS notice: List of supporting data and information in your GRAS notice (170.255)

Other Information

Did you include any other information that you want FDA to consider in evaluating your GRAS notice?

☐ Yes ☒ No

Did you include this other information in the list of attachments?

☐ Yes ☐ No

SECTION F – SIGNATURE AND CERTIFICATION STATEMENTS

1. The undersigned is informing FDA that Nestle Nutrition

(name of notifier)

has concluded that the intended use*(s)* of Medium Chain Triacylglycerol

(name of notified substance)

described on this form, as discussed in the attached notice, is (are) not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act based on your conclusion that the substance is generally recognized as safe recognized as safe under the conditions of its intended use in accordance with § 170.30.

2. Nestle Nutrition agrees to make the data and information that are the basis for the conclusion of GRAS status available to FDA if FDA asks to see them; agrees to allow FDA to review and copy these data and information during customary business hours at the following location if FDA asks to do so; agrees to send these data and information to FDA if FDA asks to do so.

(name of notifier)

Office of JHeimbach LLC at 923 Water Street #66, Port Royal VA 22535

(address of notifier or other location)

The notifying party certifies that this GRAS notice is a complete, representative, and balanced submission that includes unfavorable, as well as favorable information, pertinent to the evaluation of the safety and GRAS status of the use of the substance.The notifying party certifies that the information provided herein is accurate and complete to the best or his/her knowledge. Any knowing and willful misinterpretation is subject to criminal penalty pursuant to 18 U.S.C. 1001.

3. Signature of Responsible Official, Agent, or Attorney	**Printed Name and Title**	**Date (mm/dd/yyyy)**
	James T. Heimbach, Ph.D.	11/03/2021

SECTION G – LIST OF ATTACHMENTS

List your attached files or documents containing your submission, forms, amendments or supplements, and other pertinent information. Clearly identify the attachment with appropriate descriptive file names (or titles for paper documents), preferably as suggested in the guidance associated with this form. Number your attachments consecutively. When submitting paper documents, enter the inclusive page numbers of each portion of the document below.

Attachment Number	Attachment Name	Folder Location (select from menu) (Page Number(s) for paper Copy Only)
	Form3667.pdf	Administrative
	MCTGRASinExemptIF.pdf	Administrative
	ConclusionwithSignatureHeimbach.pdf	Administrative
	SignatureBorzelleca.pdf	Administrative
	SignatureNicolosi.pdf	Administrative

From: James Heimbach
To: Morissette, Rachel
Subject: [EXTERNAL] RE: follow-up on questions for GRN 001049
Date: Tuesday, June 28, 2022 10:08:59 AM
Attachments: image001.png
image002.png
image003.png
image004.png
image005.png
image006.png
image008.png
Nestle Gerber Response MCT GRN 1049.pdf

Dear Rachel—

Nestle has not yet been able to prepare responses to all of FDA's questions. Attached are those that have been prepared to date.

Thank you for your patience!

Regards,
Jim
James T. Heimbach, Ph.D., F.A.C.N.
JHeimbach LLC
923 Water Street #66
Port Royal VA 22535
USA
Tel: (+1) 804-742-5543
Cell: (+1) 202-320-3063
Email: jh@jheimbach.com

From: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sent: Monday, June 27, 2022 8:49 AM
To: Jim <jheimbach@va.metrocast.net>
Subject: follow-up on questions for GRN 001049

Hi Jim,

We did not receive responses to our questions for GRN 001049 sent May 31st. Is the company still planning to move ahead with this notice?

Thanks,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist/Biologist

Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

From: Morissette, Rachel
Sent: Friday, June 3, 2022 11:00 AM
To: Jim <jheimbach@va.metrocast.net>
Subject: RE: [EXTERNAL] Re: questions for GRN 001049

Thanks, Jim!

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist/Biologist

Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

From: Jim <jheimbach@va.metrocast.net>
Sent: Friday, June 3, 2022 10:59 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Subject: [EXTERNAL] Re: questions for GRN 001049

Yes I would save them. Sorry for not responding. Jim

Sent from my iPhone

> On Jun 3, 2022, at 9:21 AM, Morissette, Rachel <Rachel.Morissette@fda.hhs.gov> wrote:
>
> Hi Jim,
>
> Just want to confirm that you received the questions I sent for GRN 1049 on Tuesday.
>
> Best,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist/Biologist

Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

From: Morissette, Rachel
Sent: Tuesday, May 31, 2022 9:03 AM

To: Jim Heimbach <jheimbach@va.metrocast.net>
Subject: questions for GRN 001049

Hi Jim,

Please see attached our questions for GRN 001049.

Best regards,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist/Biologist

Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

RESPONSES TO FDA QUESTIONS ON GRN 001049

Chemistry: 1.

Q: The intended use is unclear and is described differently in different parts of the notice. For example, page 6 of the notice states: “MCT is intended to be added to exempt infant formulas intended for infants born at term, including those formulas for infants with cow's milk protein allergy, food allergies, and fat malabsorption.” However, page 12 of the notice states: “MCT is intended for use in powdered milk-based exempt infant formulas intended for infants with fat malabsorption issues.” Please clarify both the intended infant populations and the protein base of the intended infant formula.

A: MCT is intended for use as an ingredient in exempt infant formulas intended for infants born at term, including but not limited to those formulas intended for consumption by infants with cow’s milk protein allergy, multiple food allergies, and /or fat malabsorption.

These exempt infant formulas are typically composed of extensively hydrolyzed milk proteins (whey and/or casein) or amino acid based.

2. Please identify and provide citations, if available, to the analytical methods used as part of the specifications for MCT. In addition, please confirm that the methods employed are validated for the intended purpose.

We confirm that all analytical methods have been validated for the specific purposes for which they were used.

3. Nestlé states that MCT may contain minor amounts of hexanoic (C6:0), dodecanoic (C12:0), and tetradecanoic (C14:0) acids in Section 2.1 (Chemical Name, p. 8) and includes limits for C6:0 and C12:0 in Section 2.6 (Specifications, p. 10). Please confirm whether there is a specified limit for C14:0.

A: The specified limit for C:14 is 1 g/100 g.

4. We note that the results for contaminants and heavy metals in Table 1 (p. 10) are reported as “max” with an accompanying value. Please clarify if these values represent a limit of quantitation/detection. In addition, we note that the results for the sum of PCBs are listed as “max 1.0” whereas the specified limit is ≤0.75 ng/g. Please address this discrepancy.

WORKING ON THIS

5. The results from batch analyses of MCT for aerobic mesophilic organisms and coagulase positive staphylococci are listed as “NA.” Please clarify if “NA” indicates that the test was not performed or that the test resulted in a non-detect.

WORKING ON THIS

6. We note that the stability of MCT is not discussed in the notice. Please provide a discussion of the stability of MCT, including any stability studies conducted with the MCT produced by the method described in the notice.

A: MCT oil is composed primarily of saturated fatty acids, making oxidation less of a concern. The degradation reaction relevant for MCT is hydrolysis, *i.e*., formation of free fatty acids. Levels of free fatty acids are limited in the specification and the oil must have acceptable sensory characteristics.

Free fatty acids associated with C8:0 and C10:0, the two fatty acids of MCT oil, have a strong off-flavor. We do not observe these off-flavors on formulas containing MCT oil. Thus, we have indirect data suggesting good chemical stability of MCT in infant formulas.

Additionally, manufacturers must provide stability testing data and rationale when registering an infant formula for sale in the US market.

7. Nestlé provides two estimates of dietary exposure to MCT that are based on: 1) a typical intake volume of 700 mL/day and body weight (bw) of 4 kg and 2) reported energy intake for the subpopulation of infants (14-27 days of age) expected to have the highest energy intake on a bw basis.

a. Please provide a reference for the estimated daily intake of infant formula (i.e., 700 mL/day) and clarify the age group that is represented by the 4 kg bw used in Nestlé's calculation.

b. Although Nestlé's estimates for the 14-27 days-old age group are intended to represent the highest consuming subpopulation on a bw basis, Nestlé does not discuss the estimated dietary exposure to MCT for other age groups within the expected consumer population (e.g., infants up to 12 months of age).

Please provide the appropriate narrative.

A: We think it may be more representative to assume an average formula intake of 800 ml/day – based on this an infant will consume 13.6 -16.24g MCT oil per day.

B. Since the composition of the formula does not change, exposure to MCT per kcal formula consumed will remain constant. Thus, FDA's question reduces to asking what is the change in kcal/kg bw/day by age group. These data can be read directly from Fomon (1993) up to age 168-195 days, with the relevant data summarized in the following table. Note that the highest levels of intake at the 90th-centile are among boys and girls aged 14-27 days, as cited in the GRN.

Age Range (Days)	Mean kcal/kg bw/day		90th Centile kcal/kg bw/day	
	Boys	Girls	Boys	Girls
8-13	113.8	111.9	136.7	135.5
14-27	121.1	117.8	141.3	138.9
28-41	117.9	115.2	136.9	136.8
42-55	110.5	108.8	129.0	127.4
56-83	101.0	101.1	115.6	114.4
84-111	94.7	95.7	106.1	106.8
112-139	94.4	96.6	112.1	113.1
140-167	95.4	94.2	113.1	113.3
168-195	91.5	91.2	108.5	107.9

c. Nestlé states that the intended use of MCT is in exempt infant formulas intended for term infants with cow milk protein allergy, food allergies, and fat malabsorption. Please confirm that the data used for the estimates of dietary exposure are representative of this infant population.

The caloric needs of infants with cow milk protein allergy, food allergies, and fat malabsorption do not differ from those of infants without these conditions. The presence of milk protein allergy or other food allergies does not affect the quantity of formula required to meet these caloric needs. In the case of infants with fat malabsorption, the formula intake required to reach their caloric needs may be impacted by the proportion of calories provided by malabsorbed fats such as long-chain fatty acids. Since the formula under discussion replaces much of the LCFA with MCFA, which is more readily

absorbed, the impact should be slight in this case and the estimates of dietary exposure provided are expected to be representative of this population.

In a clinical study measuring growth outcomes, infants with cow's milk protein allergy were fed an extensively hydrolyzed whey based infant formula. Enrollment age varied between 0-6 months (mean age at enrollment was about 3 months). Infants were then seen monthly through 12 months of age. At V1 intake was reported at about 862 ml (29 oz). (Vandenplas 2022)

8. 3-Monochloropropane-1,2-diol esters (3-MCPDE) and glycidyl esters (GE) are chemical contaminants formed during the refining process of edible oils that have been identified in infant formula.[1] JECFA established a PMTDI for 3-MCPD and 3-MCPD esters of 4 µg/kg bw/day2 and EFSA derived a TDI of 2 µg/kg bw/day for 3-MCPD and its esters.[3] JECFA and EFSA have also reviewed GE and consider glycidol to be a potential genotoxic carcinogen.[2,4] The manufacture of MCT in GRN 001049 includes the use of fatty acids obtained from food-grade seed or vegetable oils, including coconut and palm kernel oils. Based on the specified limits provided for MCPDE and GE in MCT (Table 1, p. 10), given the stated toxicity concerns, and recent efforts to reduce dietary exposure to 3-MCPDE and GE in products obtained from refined oils, please provide a narrative that supports the safe use of MCT for the intended uses. A discussion of mitigation strategies can be found in the Codex Code of Practice entitled "Reduction of 3-monochloropropane-1,2-diol esters (3- MCPDE) and glycidyl esters (GE) in Refined Oils and Food Products Made with Refined Oils" (adopted July 2019, 42nd session, Codex Alimentarius Commission).[5]

A: The maximum value for 3-MCPD bound in esters must remain at 0.35 mg/kg. However, the specification for 3-MCPD in MCT oil for use in infant formula should have been expressed as a maximum of 0.1 mg/kg.

Based on the level submitted in the GRAS, intake of MCT is expected to be 13.6 – 16.24 g a day assuming an average intake of 800 mL formula. The maximum amount of glycidol esters considering a specification maximum of 0.1 mg/kg would be 0.48 mcg/kg bw/day. For MCPD at a maximum of 0.35 mg/kg, the intake would be 1.66 mcg/kg bw /day. Combined, the level would be a maximum of 2.13 mcg/kg/bw /day assuming a 3.4 kg infant at months of age consuming 800 mL of formula.

Toxicology:

9. The notice does not discuss the impact of dietary MCT on potential carnitine depletion in term and preterm infants. Given that there is currently no regulatory minimum requirement for the addition of L-carnitine in exempt infant formula, please discuss how the potential depletion of carnitine levels in infants consuming higher levels of MCT would not be a safety concern from the intended use, especially for those infants suffering from fat malabsorption.

WORKING ON THIS

10. The notice states on p. 97 “A comprehensive search of the literature through December 2020 served as the basis for preparation of a monograph summarizing the information available germane to determining the safety of the intended use of MCT in exempt infant formulas.” Please confirm that no new publicly available information pertinent to Nestlé’s GRAS conclusion has been found since December 2020

No new information relevant to the GRAS conclusion has appeared in the published literature since 2020. While there has been a number of published research articles involving infants, they have all focused on preterm infants and low-birth-weight preterm infants. Furthermore, these studies have shown an absence of adverse effects that might call the GRAS conclusion into question.

From:	Callen,Cheryl,US-Arlington
To:	Morissette, Rachel
Cc:	James Heimbach
Subject:	[EXTERNAL] RE: requesting follow-up on questions for GRN 001049
Date:	Friday, July 22, 2022 2:01:20 PM
Attachments:	image001.png image002.png image003.png image004.png image005.png image006.png image008.png Nestle Response GRAS Review MCT L-carnitine 7.20.pdf

---

Hi Rachel,
Attached are the responses to the remaining questions.

Regards,
Cheryl

From: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sent: Thursday, July 21, 2022 2:15 PM
To: Callen,Cheryl,US-Arlington <Cheryl.Callen@us.nestle.com>; James Heimbach <jheimbach@va.metrocast.net>
Subject: RE: [EXTERNAL] RE: requesting follow-up on questions for GRN 001049

Thanks, Cheryl!

Best regards,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist/Biologist

Division of Food Ingredients
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rachel.morissette@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

From: Callen,Cheryl,US-Arlington <Cheryl.Callen@us.nestle.com>
Sent: Thursday, July 21, 2022 12:09 PM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>; James Heimbach <jheimbach@va.metrocast.net>
Subject: [EXTERNAL] RE: requesting follow-up on questions for GRN 001049

Hi Rachel,
Thanks for following up. I will be sending a response by tomorrow.

Regards,
Cheryl

From: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sent: Thursday, July 21, 2022 11:09 AM
To: James Heimbach <jheimbach@va.metrocast.net>
Cc: Callen,Cheryl,US-Arlington <Cheryl.Callen@us.nestle.com>
Subject: requesting follow-up on questions for GRN 001049

Dear Jim,

I am following up on my email from last Friday as a reminder. I want to make sure my emails are getting through, since we've reached out a few times but haven't heard back.

Best regards,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist/Biologist

Division of Food Ingredients
Office of Food Additive Safety

Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

From: Morissette, Rachel
Sent: Friday, July 15, 2022 10:13 AM
To: James Heimbach <jheimbach@va.metrocast.net>
Subject: RE: [EXTERNAL] RE: follow-up on questions for GRN 001049

Dear Jim,

I haven't heard back regarding Nestle's responses to our questions. Please let us know by COB July 22 if Nestle intends to ask us to cease to evaluate GRN 1049. Otherwise we'll need to proceed with a no basis letter if we don't receive a response.

Best regards,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist/Biologist

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rachel.morissette@fda.hhs.gov

From: Morissette, Rachel
Sent: Wednesday, July 13, 2022 12:26 PM
To: James Heimbach <jheimbach@va.metrocast.net>
Subject: RE: [EXTERNAL] RE: follow-up on questions for GRN 001049

Hi Jim,

Any updates on the rest of Nestle's responses?

Thanks,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist/Biologist

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Office of Food Additive Safety
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rachel.morissette@fda.hhs.gov

From: James Heimbach <jheimbach@va.metrocast.net>
Sent: Wednesday, June 29, 2022 11:10 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Subject: RE: [EXTERNAL] RE: follow-up on questions for GRN 001049

Rachel—

Nestle informs me that they need about a week. Once again, thanks for your patience.

Jim

From: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sent: Tuesday, June 28, 2022 10:21 AM
To: James Heimbach <jheimbach@va.metrocast.net>
Subject: RE: [EXTERNAL] RE: follow-up on questions for GRN 001049

Thank you, Jim. Can you please let us know when we can expect the rest of the responses from Nestle?

Best,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist/Biologist

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rachel.morissette@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

I GOT MY COVID-19 VACCINATION

From: James Heimbach <jheimbach@va.metrocast.net>
Sent: Tuesday, June 28, 2022 10:08 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Subject: [EXTERNAL] RE: follow-up on questions for GRN 001049

Dear Rachel—

Nestle has not yet been able to prepare responses to all of FDA's questions. Attached are those that have been prepared to date.

Thank you for your patience!

Regards,
Jim
James T. Heimbach, Ph.D., F.A.C.N.
JHeimbach LLC
923 Water Street #66
Port Royal VA 22535
USA
Tel: (+1) 804-742-5543
Cell: (+1) 202-320-3063
Email: jh@jheimbach.com

From: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sent: Monday, June 27, 2022 8:49 AM
To: Jim <jheimbach@va.metrocast.net>
Subject: follow-up on questions for GRN 001049

Hi Jim,

We did not receive responses to our questions for GRN 001049 sent May 31st. Is the company still planning to move ahead with this notice?

Thanks,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist/Biologist

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rachel.morissette@fda.hhs.gov

From: Morissette, Rachel
Sent: Friday, June 3, 2022 11:00 AM
To: Jim <jheimbach@va.metrocast.net>
Subject: RE: [EXTERNAL] Re: questions for GRN 001049

Thanks, Jim!

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist/Biologist

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U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

From: Jim <jheimbach@va.metrocast.net>
Sent: Friday, June 3, 2022 10:59 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Subject: [EXTERNAL] Re: questions for GRN 001049

Yes I would save them. Sorry for not responding. Jim

Sent from my iPhone

> On Jun 3, 2022, at 9:21 AM, Morissette, Rachel <Rachel.Morissette@fda.hhs.gov> wrote:
>
> Hi Jim,

Just want to confirm that you received the questions I sent for GRN 1049 on Tuesday.

Best,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist/Biologist

Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

From: Morissette, Rachel
Sent: Tuesday, May 31, 2022 9:03 AM
To: Jim Heimbach <jheimbach@va.metrocast.net>
Subject: questions for GRN 001049

Hi Jim,

Please see attached our questions for GRN 001049.

Best regards,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist/Biologist

Division of Food Ingredients
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Center for Food Safety and Applied Nutrition
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rachel.morissette@fda.hhs.gov


FDA
U.S. FOOD & DRUG
ADMINISTRATION


I GOT MY
COVID-19
VACCINATION

FDA Question #4:

We note that the results for contaminants and heavy metals in Table 1 (p. 10) are reported as "max" with an accompanying value. Please clarify if these values represent a limit of quantitation/detection. In addition, we note that the results for the sum of PCBs are listed as "max 1.0" whereas the specified limit is ≤0.75 ng/g. Please address this discrepancy.

Nestle Response

The last three columns in the table represent the maximum values for the heavy metals. These values do not represent the limit of quantification. We are in process of obtaining actual test results for 3 batches of MCT oil to confirm the values.

The 0.75 ng/g for the sum of PCBs is a mistake. We apologize for this. The value should be 20 ng/g.

Parameter	Unit	Specification	Batch/Lot Number		
			0002238522	0002233943	0002226170
Sensory					
Appearance		Oily liquid			
Color		Pale to light yellow	Clear	Clear	Clear
Odor		Bland	Neutral	Neutral	Neutral
Taste		Neutral, bland	Neutral	Neutral	Neutral
Physical Chemical					
Moisture	g/100 g	≤ 0.1	0.03	0.01	0.03
Acid value	mg KOH/g	≤ 0.1	0	0.02	0
Free fatty acids as lauric acid	g/100 g	≤ 0.05	0	0.01	0
Peroxide value ex works	meq. O_2/kg	≤ 0.5	<0.1	<0.1	<0.1
Hexanoic acid C6:0	g/100 g	≤ 1.8	0.1	<0.1	<0.1
Octanoic acid C8:0	g/100 g	40 - 60	57.8	58.3	57.0
Decanoic acid C10:0	g/10 0g	20 - 50	32.7	35.6	33.5
Lauric acid C12:0	g/100 g	≤ 1.5	0.2	<0.1	0.2
Iodine value	cg/g	≤ 0.5	0.0	0.0	0.0
Contaminants					
3-MCPD bound in esters	mg/kg	≤ 0.35	0.17	0.26	0.29
Glycidol bound in esters	mg/kg	≤ 0.30	<0.1	<0.1	<0.1
Sum of dioxins and furans (WHO-PCDD/F-TEQ)	pg/g	≤ 0.75	Max 0.3	Max 0.3	Max 0.3
Sum of dioxins, furans and dioxin-like PCBs (WHO-PCDD/F-PCB-TEQ)	pg/g	≤ 1.25	Max 0.5	Max 0.5	Max 0.5
Sum of polychlorinated biphenyls (PCBs) 28, 52, 101, 138, 153 and 180	ng/g	≤ 0.75	Max 1.0	Max 1.0	Max 1.0
Benzo(a)pyrene	µg/g	≤ 2.0	Max 1.0	Max 1.0	Max 1.0
Sum of benzo(a)pyrene, benz(a)anthracene, benzo(b)fluoranthene and chrysene (PAH 4)	µg/g	≤ 3.0	Max 2.0	Max 2.0	Max 2.0
Heavy Metals					
Arsenic	mg/kg	≤ 0.1	Max 0.1	Max 0.1	Max 0.1
Cadmium	mg/kg	≤ 0.02	Max 0.005	Max 0.005	Max 0.005
Lead	mg/kg	≤ 0.1	Max 0.01	Max 0.01	Max 0.01
Mercury	mg/kg	≤ 0.05	Max 0.01	Max 0.01	Max 0.01

FDA Question #5:

The results from batch analyses of MCT for aerobic mesophilic organisms and coagulase positive staphylococci are listed as “NA.” Please clarify if “NA” indicates that the test was not performed or that the test resulted in a non-detect.

Nestle Response

We believe the test was not performed though we have not yet confirmed this point. These are not typical tests for oils as they are devoid of moisture (max. 0.1%) and fully refined which includes deodorization, a HTLT (high temperature-long time) treatment including temperatures above 200 °C, steam injection and low vacuum (absolute pressure max. 5 mbar) making them sterile at the end of

refining. In addition, the MCT is added to infant formula in the wet mix process prior to the critical control point for heat treatment.

FDA Question #9:

The notice does not discuss the impact of dietary MCT on potential carnitine depletion in term and preterm infants. Given that there is currently no regulatory minimum requirement for the addition of L-carnitine in exempt infant formula, please discuss how the potential depletion of carnitine levels in infants consuming higher levels of MCT would not be a safety concern from the intended use, especially for those infants suffering from fat malabsorption.

Nestlé Response

Carnitine is an amino acid that is not incorporated into protein and can be synthesized by the body from cysteine. Normal carnitine levels are maintained by balance between dietary intake, endogenous synthesis, and renal reabsorption (Almannai, 2019). Rates of synthesis in infants fed parenterally or those receiving formulas devoid of carnitine may be insufficient to meet their needs (Kleinman 2014). In fat metabolism, carnitine acts as a carrier of long chain fatty acids into mitochondria whereas medium chain triglycerides do not require carnitine for transport into the mitochondria (Shah 2017). Although the role of carnitine does not include the actual transport of medium-chain fatty acids into the mitochondria, it could involve the export of partially oxidized fatty acids from the cell in an effort to free bound coenzyme A (speculated by Wade 1991).

Los-Rycharska (2016) stated that quantities of MCT exceeding the abilities of the liver to metabolize it are metabolised peripherally in a carnitine-dependent mechanism, which can increase the demand for carnitine. The same authors stated that some adverse effects of formulas containing high proportion of MCT described in literature include deficiency of carnitine resulting in damage of the liver and kidneys due to long-lasting feeding of a prematurely born infant (24 Hbd) with extremely low body mass. It has also been found that MCT can engage carnitine in the course of their metabolism and carnitine reserves in infants are low. Therefore, in such cases supplementation with carnitine should be considered (Los Rycharska, 2016). Because of this, in some mitochondrial carnitine-acylcarnitine cycle disorders, use of MCT for long-term management may be recommended (Almannai 2019).

Premature infants can be at-risk for carnitine deficiency as preterm infants are more likely to suffer from metabolic abnormalities. There has been a report of liver and kidney damage secondary to carnitine deficiency in a premature infant born at 24 weeks (Ishida 1994) fed a formula containing 17.3 g and 15 mg carnitine/100g powder for 40 days that was treated effectively with administration of L-carnitine. While this case study of a premature infant reported an effect on plasma carnitine levels linked to use of an MCT-containing infant formula, in a short study of 12 preterm infants fed LCT or an MCT/LCT emulsion parenterally, free carnitine and acylcarnitine concentrations were similar in the two groups, and neither free carnitine nor total carnitine or individual acylcarnitines decreased significantly from day 1 to day 8 in either group (Lehner 2006). There were no appreciable differences in plasma free carnitine and acylcarnitine values between the two groups.

There has been one study in the literature of term infants orally fed medium chain triglycerides (Rebouche 1990). In protocol 1, five infants (173-234 d) were fed Enfamil (2.7 g MCT/L, 132 umol/L carnitine) and Enfamil Premature formula (14.8g MCT/L, 185 umol/L carnitine). Subjects were fed Enfamil for study days 1-7 and then switched to the premature formula for days 7-14. On day 15, subjects were switched back to regular Enfamil and then back to the premature formula for days 23-29.

In protocol 2, 20 infants (21-186 d) were fed a soy formula containing 40% of energy as fat as MCT with (61.2-65.4 umol/L) or without (<1umol/L) L-carnitine for 56 days. Infants were fed ad libitum in both studies and were introduced to semisolid foods at 140 days of age. In study 1, plasma carnitine concentrations (free and total) were unchanged by the feeding regimen. Urinary free and total carnitine excretion were not affected by feeding regimen. In study 2, plasma carnitine concentrations were higher at 28 and 56 days in the formula supplemented with carnitine than the one without. Urinary free and total carnitine excretion were greater in the carnitine-supplemented formula. There were no reports of evidence of carnitine deficiency in any of these studies. The authors deduced that carnitine promotes efficient utilization of MCFAs by acting as a sink for short-chain acyl moieties generated by beta-oxidation, thus increasing the availability of free coenzyme A and providing a means for removal of excess acetyl groups from mitochondria and perhaps cells to be able to recycle CoA.

There are no requirements for specific levels of carnitine supplementation for infant formula nor sufficient studies to establish whether MCT-containing infant formula may cause carnitine deficiency. While few studies exist looking at the impact of dietary MCT on carnitine depletion in term and preterm infants, there is a risk of this occurring as reported in the case study by Ishida (1994). However, to the best of our knowledge, this was the only case report found in the literature. In the study of full-term infants fed MCT-containing formula (40% of fat from MCT), there were no reports of carnitine deficiency, even in the group that was fed the formula without L-carnitine (Rebouche 1990).

Exempt infant formulas designed for infants with severe allergy and gut malabsorption contain MCT as an important source of fat. We are not aware of any reports of carnitine deficiency with the use of exempt infant formulas with MCT and supplemental carnitine.

Below is a summary of MCT and L-Carnitine levels per 100 grams and per Liter for Nestle Alfamino Infant, Alfamino Junior, and Gerber Extensive HA.

Alfamino infant and Alfamino Junior formulas are hypoallergenic amino acid-based formulas intended for infants (ages 0 to 12 months) and children (ages 1 to 13 years) with cow's milk protein allergy, multiple food protein allergies, and/or conditions of gastrointestinal malabsorption.

Extensive HA is a hypoallergenic extensively hydrolyzed whey-based formula intended for infants (ages 0 to 12 months) with cow's milk protein allergy, milk intolerance, sensitivity to intact cow's milk and/or soy protein, cow's milk-induced food protein induced enterocolitis syndrome, and infants with fat malabsorption.

Product	**MCT g/100g**	**MCT g/L**	**L-Carnitine g/100g**	**L-Carnitine mg/L**
Alfamino Infant formula	10.8	14.3	0.007	9.3
Extensive HA Infant formula	12.5	17	0.007	9.5
Alfamino Junior Unflavored	13	28	0.014	30
Alfamino Junior Vanilla	13	28	0.014	30

References:

Almannai M, Alfadehl M, El-Hattab AW. Carnitine Inborn Errors of Metabolism. Molecules 2019;24:3251; doi:10.3390/molecules24183251.

Kleinman RE, ed. Pediatric Nutrition Handbook. 7th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2014.

IshidaA, Goto A, Takahashi Y, et al. A Preterm Infant with Deficiency due to MCT - Effective Treatment Secondary Carnitine Formula of L-Carnitine. Tohoku J Exp Med 1994;172:59-64.

Łoś-Rycharska E, Kieraszewicz Z, Czerwionka-Szaflarska M. Medium chain triglycerides (MCT) formulas in paediatric and allergological practice. Gastroenterology Rev 2016;11:226–231.

Rebouche CJ, Panagides DD, Nelson SE. Role of carnitine in utilization of dietary medium-chain triglycerides by term infants. American Journal of Clinical Nutrition 1990;52:820-4.

Shah ND, Lemketkai BN. The Use of Medium-Chain Triglycerides in Gastrointestinal Disorders. Practical Gastroenterology 2017;160:20-28.

Wade LA. A role for carnitine in medium-chain fatty acid metabolism? Nutrition Reviews 1991;49:243-245.

From: Callen,Cheryl,US-Arlington
To: Morissette, Rachel
Cc: Jim Heimbach
Subject: RE: [EXTERNAL] RE: additional questions for GRN 001049
Date: Friday, September 2, 2022 12:25:09 PM
Attachments: image001.png
image002.png
image003.png
image004.png
image005.png
image006.png
image008.png
image009.png
MCT GRN Specifications Chem Physical 8.31.2022.docx

Hi Rachel,
Below are responses to your questions. We are also including an updated MCT specification table – which has the method references; updated data; and errors corrected. Note a few of the references are internal- I will have copies of those next week.

1. In question 2 from the June 28, 2022 amendment, we requested that Nestle "Identify and provide citations, if available, to the analytical methods used as part of the specifications for MCT. In addition, please confirm that the methods employed are validated for the intended purpose." Nestle confirmed that all analytical methods are validated for the specific purposes for which they are used. However, the identity of the methods used and citations to applicable published methods were not provided. Please provide those citations or clarify why they are not available.

We are providing an updated specification table with citations for the methods used. Please let us know if more details are needed. For those listed as "Oleon", these are internal methods and we will have copies of those methods by next week.

2. In Nestle's response to question 8 from the June 28, 2022 amendment, Nestle stated that "The maximum value for 3-MCPD bound in esters must remain at 0.35 mg/kg. However, the specification for 3-MCPD in MCT oil for use in infant formula should have been expressed as a maximum of 0.1 mg/kg." Please clarify if the limit of 0.1 mg/kg is for 3-MCPD or for GE.

We apologize for the confusion- the limit of 0.1 mg.kg is for GE. We are providing an updated specification table, which has corrected the previous errors, includes method citations and provides updated data for new batches of this ingredient.

3. In response to question 4 in the July 22, 2022 amendment, Nestle stated that the reported values represent the maximum values for the heavy metals; however, the values do not represent the limit of quantification. Additionally, Nestle stated they are in the process of obtaining actual test results for the three batches of MCT oil to confirm the values. Please provide an update or clarify whether Nestle is intending to submit additional information to FDA regarding these batch analyses.

We have providing an updated specification table, which has corrected the previous errors, includes method citations and provides updated data for new batches of this ingredient.

Please let us know if there are any additional questions. Hope you have a great long weekend!

Regards,
Cheryl

From: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sent: Friday, August 19, 2022 2:05 PM
To: Callen,Cheryl,US-Arlington <Cheryl.Callen@us.nestle.com>; Jim Heimbach <jheimbach@va.metrocast.net>
Subject: RE: [EXTERNAL] RE: additional questions for GRN 001049

Thank you!

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist/Biologist

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rachel.morissette@fda.hhs.gov

From: Callen,Cheryl,US-Arlington <Cheryl.Callen@us.nestle.com>
Sent: Friday, August 19, 2022 2:04 PM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>; Jim Heimbach <jheimbach@va.metrocast.net>
Subject: [EXTERNAL] RE: additional questions for GRN 001049

Hi Rachel
Thanks for your mail. We are planning to provide additional data – I am in process of getting the data and hope to have within the next 2 weeks.

Let me know any questions.

Regards,
Cheryl

From: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sent: Friday, August 19, 2022 1:36 PM
To: Jim Heimbach <jheimbach@va.metrocast.net>
Cc: Callen,Cheryl,US-Arlington <Cheryl.Callen@us.nestle.com>
Subject: additional questions for GRN 001049

Dear Jim,

Please see some additional questions below from our chemist regarding Nestle's June 28, 2022 and July 22, 2022 amendments:

1. In question 2 from the June 28, 2022 amendment, we requested that Nestle "Identify and provide citations, if available, to the analytical methods used as part of the specifications for MCT. In addition, please confirm that the methods employed are validated for the intended purpose." Nestle confirmed that all analytical methods are validated for the specific purposes for which they are used. However, the identity of

the methods used and citations to applicable published methods were not provided. Please provide those citations or clarify why they are not available.

2. In Nestle's response to question 8 from the June 28, 2022 amendment, Nestle stated that "The maximum value for 3-MCPD bound in esters must remain at 0.35 mg/kg. However, the specification for 3-MCPD in MCT oil for use in infant formula should have been expressed as a maximum of 0.1 mg/kg." Please clarify if the limit of 0.1 mg/kg is for 3-MCPD or for GE.

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Please let me know if you have any questions.

Best regards,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist/Biologist

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MCT Specifications **Revised 8/31/2022**

Parameter	Unit	Specification	Batch /Lot Number			Method
			KL90823X08 6308	OE10113T01 7162	OE11019T01 6773	
Appearance		Oily liquid	meets	meets	meets	Oleon)S-200
Color		Pale to light yellow	meets	meets	meets	
Odor		Neutral	meets	meets	meets	Oleon OS-053
Taste		Bland, neutral				
Moisture	g/100g	≤0.1	0.01	0.02	0.04	AOCS Ca 2e-84
Acid value	mg KOH/g	≤0.1	0.01	0.09	0.02	AOCS Cd 3d-63
Free fatty acids as lauric acid	g/100g	≤0.05	0.01	0.02	0.01	AOCS Cd 3d-63
Peroxide value	meq O_2/kg	≤0.5	<0.2	<0.20	0.20	AOCS Cd 8b-90
Hexanoic acid C6:0	g/100g	≤1.8	0	0	0	AOCS-Ce 1-62
Octanoic Acid C8:0	g/100g	40-60	56	55.1	60.2	AOCS Ce 1-62
Decanoic Acid C10:0	g/100g	20-50	43.6	44.5	39.6	AOCS Ce 1-62
Lauric Acid C12:0	g/100g	≤1.5	0.2	0.1	0.1	AOCS Ce 1-62
Tetradecanoic C14:0	g/100g	1	0	0	0	AOCS Ce 1-62
Iodine Value	cg/g	≤0.5	0.12	0.10	0.06	Oleon OA-020
3 MCPD bound in esters	mg/kg	≤0.35	< 0.35	<0.10	0.06	AOCS Cd 29b-13
Glycidol bound in esters	mg/kg	≤0.1	< 0.1	<0.10	<0.05	AOCS Cd 29b-13
Sum of dioxins and furans (WHO- PCDD/F-TEQ)	pg/g	≤0.75	0.061	0.062	0.061	EPA 1613 B 1994 +Reg CEE 1259/2011 02/12/2011 GU CE L320 03/12/2011 EPA 1613 B 1994 +REG UE 277/2012 28/03/2012 GU UE L91 29/03/2012
Sum of dioxins and furans and dioxin like PCBs (WHO-PCDD/F-PCB-TEQ)	pg/g	≤1.25	0.078	0.078	0.078	EPA 1668 C 2010 + REG CEE 1259/2011 02/12/2011 GU CE L320 03/12/2011 EPA 1668 C 2010 + REG UE 277/2012 28/03/2012 GU UE L91 29/03/2012
Sum of polychlorinated biphenyls (PCBs) 28, 52, 101,138, 153, 180	ng/g	≤20	0.008	0.008	0.015	EPA 1668 C 2010 + REG CEE 1259/2011 02/12/2011 GU CE L320 03/12/2011 EPA 1668 C 2010 + REG UE 277/2012 28/03/2012 GU UE L91 29/03/2012
Benzo(a) pyrene	µg/g	≤2.0	<LQ	<LQ	<LQ	PNA 2019 Rev 5- GC-MS or 04 (S84) 2021 Rev 7 GC-MS-MS
Sum of Benzo(a) pyrene, benz(a)anthracene,benzo(b) fluoranthene, chrysene (PAH 4)	µg/g	≤3.0	<LQ (measured individually)	<LQ (measured individually)	<LQ (measured individually)	PNA 2019 Rev 5- GC-MS or 04 (S84) 2021 Rev 7 GC MS MS
					<LQ	05(ICP-MS) 2018 Rev 3 or

						05 (ICP-MS) 2021 Rev 4 (ICP-MS)
Cadmium	mg/kg	≤0.02	<LQ	<LQ	<LQ	05(ICP-MS) 2018 Rev 3 or 05 (ICP-MS) 2021 Rev 4 (ICP-MS)
Lead	mg/kg	≤0.1	<LQ	<LQ	<LQ	05(ICP-MS) 2018 Rev 3 or 05 (ICP-MS) 2021 Rev 4 (ICP-MS)
Mercury	mg/kg	≤0.05	<LQ	<LQ	<LQ	05(ICP-MS) 2018 Rev 3 or 05 (ICP-MS) 2021 Rev 4 (ICP-MS)

Property	LQ Samples 6308 and 6172	LQ Sample 7162
Benzo(a) pyrene	0.50 µg/g	0.1 µg/g
Arsenic	0.005 mg/kg	0.005 mg/kg
Cadmium	0.005 mg/kg	0.005 mg/kg
Lead	0.005 mg/kg	0.005 mg/kg
Mercury	0.005 mg/kg	0.005 mg/kg

From: Callen,Cheryl,US-Arlington
To: Morissette, Rachel
Cc: Jim Heimbach
Subject: RE: [EXTERNAL] RE: additional questions for GRN 001049
Date: Friday, September 16, 2022 3:48:36 PM
Attachments: image001.png
image002.png
image003.png
image004.png
image005.png
image006.png
image007.png
image009.png
image010.png

Hi Rachel,
We are providing an updated chart to demonstrate compliance with the microbiological specifications. The chart originally submitted did not include the methods and was not specific on testing of aerobic mesophilic organisms or coagulase positive staphylococci. The new/updated chart is more clear in this regard.

NEW/UPDATED

Parameter	Specification	Batch/Lot Number			Method
		22-2389	22-1455	22-2390	
Contaminant microorganisms					
Aerobic mesophilic organisms	≤ 1,000/g	< LQ (10)	< LQ (10)	< LQ (10)	ISO 4833-1:2013
Coagulase positive staphylococci	≤10/g	< 10 (LQ)	< 10 (LQ)	< LQ (10)	ISO 6888-1:2021
Cronobacter species	Absent /10g	Absent /10g	Absent /10g	Absent /10g	ISO 22964:2017
Enterobacteriaceae	≤10/g	< 10 (LQ)	<10 (LQ)	< LQ (10)	ISO 21528-2:2017
Salmonella	Absent/25 g	Absent/25 g	Absent/25 g	Absent/25 g	ISO 6579-1:2021

CHART Originally Submitted

Parameter	**Units**	**Specification**	Lot Number		
			0002238522	0002233943	0002226170
Contaminant microorganisms					
Aerobic mesophilic organisms		≤ 1,000/g	NA	NA	NA
Coagulase positive *staphylococci*		≤ 10/g	NA	NA	NA
Cronobacter species		Absent/10 g	Absent/10 g	Absent/10 g	Absent/10 g
Enterobacteriaceae		≤ 10/g	Absent/10 g	Absent/10 g	Absent/10 g
Salmonella		Absent/25 g	Absent/25g	Absent/25g	Absent/25g

I believe the only remaining information to be provided are the methods for the sensory attributes. Please let us know if you have any other questions.

Thank you for your patience!

Regards,
Cheryl

From: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sent: Tuesday, September 13, 2022 8:58 AM
To: Callen,Cheryl,US-Arlington <Cheryl.Callen@us.nestle.com>
Cc: Jim Heimbach <jheimbach@va.metrocast.net>
Subject: RE: [EXTERNAL] RE: additional questions for GRN 001049

Thank you.

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist/Biologist

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FDA U.S. FOOD & DRUG ADMINISTRATION

I GOT MY COVID-19 VACCINATION

From: Callen,Cheryl,US-Arlington <Cheryl.Callen@us.nestle.com>
Sent: Tuesday, September 13, 2022 8:52 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Cc: Jim Heimbach <jheimbach@va.metrocast.net>
Subject: RE: [EXTERNAL] RE: additional questions for GRN 001049

Hi Rachel,
I have reached out to my Nestle contact to check on status. Hope to have an update today.

Regards,
Cheryl

From: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sent: Friday, September 9, 2022 10:41 AM
To: Callen,Cheryl,US-Arlington <Cheryl.Callen@us.nestle.com>
Cc: Jim Heimbach <jheimbach@va.metrocast.net>
Subject: RE: [EXTERNAL] RE: additional questions for GRN 001049

Dear Cheryl,

Just following up on your email from last week. Is Nestle able to send us the remaining information mentioned below?

Thanks,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist/Biologist

Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
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rachel.morissette@fda.hhs.gov

From: Callen,Cheryl,US-Arlington <Cheryl.Callen@us.nestle.com>
Sent: Friday, September 2, 2022 12:24 PM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Cc: Jim Heimbach <jheimbach@va.metrocast.net>
Subject: RE: [EXTERNAL] RE: additional questions for GRN 001049

Hi Rachel,
Below are responses to your questions. We are also including an updated MCT specification table – which has the method references; updated data; and errors corrected. Note a few of the references are internal- I will have copies of those next week.

1. In question 2 from the June 28, 2022 amendment, we requested that Nestle "Identify and provide citations, if available, to the analytical methods used as part of the specifications for MCT. In addition, please confirm that the methods employed are validated for the intended purpose." Nestle confirmed that all analytical methods are validated for the specific purposes for which they are used. However, the identity of the methods used and citations to applicable published methods were not provided. Please provide those citations or clarify why they are not available.

We are providing an updated specification table with citations for the methods used. Please let us know if more details are needed. For those listed as "Oleon", these are internal methods and we will have copies of those methods by next week.

2. In Nestle's response to question 8 from the June 28, 2022 amendment, Nestle stated that "The maximum value for 3-MCPD bound in esters must remain at 0.35 mg/kg. However, the specification for 3-MCPD in MCT oil for use in infant formula should have been expressed as a maximum of 0.1 mg/kg." Please clarify if the limit of 0.1 mg/kg is for 3-MCPD or for GE.

We apologize for the confusion- the limit of 0.1 mg.kg is for GE. We are providing an updated specification table, which has corrected the previous errors, includes method citations and provides updated data for new batches of this ingredient.

3. In response to question 4 in the July 22, 2022 amendment, Nestle stated that the reported values represent the maximum values for the heavy metals; however, the values do not represent the limit of quantification. Additionally, Nestle stated they are in the process of obtaining actual test results for the three batches of MCT oil to confirm the values. Please provide an update or clarify whether Nestle is intending to submit additional information to FDA regarding these batch analyses.

We have providing an updated specification table, which has corrected the previous errors, includes method citations and provides updated data for new batches of this ingredient.

Please let us know if there are any additional questions. Hope you have a great long weekend!

Regards,
Cheryl

From: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sent: Friday, August 19, 2022 2:05 PM

To: Callen,Cheryl,US-Arlington <Cheryl.Callen@us.nestle.com>; Jim Heimbach <jheimbach@va.metrocast.net>
Subject: RE: [EXTERNAL] RE: additional questions for GRN 001049

Thank you!

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist/Biologist

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rachel.morissette@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

I GOT MY COVID-19 VACCINATION

From: Callen,Cheryl,US-Arlington <Cheryl.Callen@us.nestle.com>
Sent: Friday, August 19, 2022 2:04 PM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>; Jim Heimbach <jheimbach@va.metrocast.net>
Subject: [EXTERNAL] RE: additional questions for GRN 001049

Hi Rachel
Thanks for your mail. We are planning to provide additional data – I am in process of getting the data and hope to have within the next 2 weeks.

Let me know any questions.

Regards,
Cheryl

From: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sent: Friday, August 19, 2022 1:36 PM
To: Jim Heimbach <jheimbach@va.metrocast.net>

Cc: Callen,Cheryl,US-Arlington <Cheryl.Callen@us.nestle.com>
Subject: additional questions for GRN 001049

Dear Jim,

Please see some additional questions below from our chemist regarding Nestle's June 28, 2022 and July 22, 2022 amendments:

1. In question 2 from the June 28, 2022 amendment, we requested that Nestle "Identify and provide citations, if available, to the analytical methods used as part of the specifications for MCT. In addition, please confirm that the methods employed are validated for the intended purpose." Nestle confirmed that all analytical methods are validated for the specific purposes for which they are used. However, the identity of the methods used and citations to applicable published methods were not provided. Please provide those citations or clarify why they are not available.

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