Toxicological profile for

Caprylic-capric triglycerides

This ingredient has been assessed to determine potential human health effects for the consumer. It was considered not to increase the inherent toxicity of the product and thus is acceptable under conditions of intended use.

1. Name of substance and physico-chemical properties

1.1. IUPAC systematic name

Decanoic acid; octanoic acid; propane-1,2,3-triol; 11-(2,3-Dihydroxypropoxycarbonyl)heptadecanoate (CAS RN 73398-61-5) (PubChem); 1-Hydroxy-3-(octanoyloxy)-2-propanyl decanoate (CAS RN 65381-09-1) (ChemSpider)

1.2. Synonyms

CAS RN 73398-61-5: EINECS 277-452-2; Glycerin, mixed triester with caprylic acid and capric acid; Glycerides, mixed decanoyl and octanoyl; Mixed decanoyl and octanoyl glycerides (ChemIDplus); Glyceryl caprylate-caprate (PubChem)

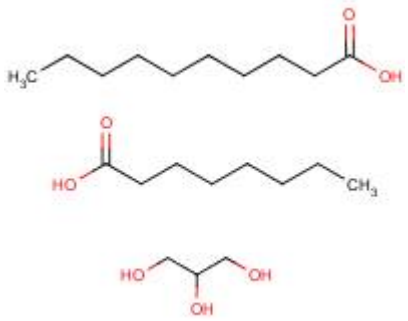
CAS RN 65381-09-1: Decanoic acid, ester with 1,2,3-propanetriol octanoate; EINECS 265-724-3; Glycerol octanoate decanoate; Caprylic/capric triglyceride; Octanoic/decanoic acid triglyceride; Caprylic acid, capric acid triglyceride (ChemIDplus)

1.3. Molecular formula

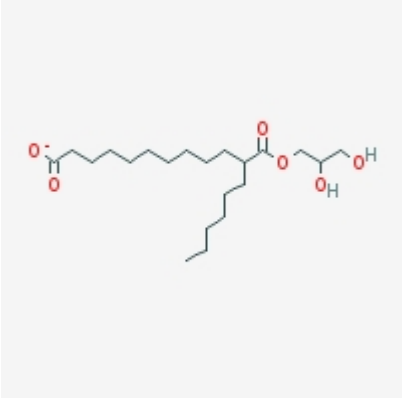
”Unspecified” (CAS RN 73398-61-5) (ChemIDplus); $C_{10}H_{20}O_2.x\text{-}C_8H_{16}O_2.x\text{-}C_3H_8O_3$ (CAS RN 65381-09-1) (ChemIDplus); $C_{21}H_{39}O_6^-$ (CAS RN 73398-61-5) (PubChem)

1.4. Structural Formula

CAS RN 65381-09-1 (ChemIDplus)



CAS RN 73398-61-5 (PubChem)



1.5. Molecular weight (g/mol)

408.572 (sum of monomers) (CAS RN 65381-09-1) (ChemIDplus); 387.5 (CAS RN 73398-61-5) (PubChem).

1.6. CAS registration number

73398-61-5, 65381-09-1

1.7. Properties

1.7.1. Melting point

CAS RN 73398-61-5: (°C): ca. 0-10 (IUCLID, 2000) **CAS RN 65381-09-1:** (°C): 66.17 (estimated) (EPISuite, 2017).

1.7.2. Boiling point

CAS RN 73398-61-5: (°C): 449.67 (estimated; for molecular formula C21H42O5) (EPISuite, 2017)
CAS RN 65381-09-1: (°C): 414.31 (estimated; for molecular formula C21H40O5) (EPISuite, 2017); 456.0±12.0 at 760 mmHg (estimated) (ChemSpider)

1.7.3. Solubility

CAS RN 73398-61-5: <10 mg/ml at 20°C in water (IUCLID, 2000) **CAS RN 65381-09-1:** 0.06951 mg/L at 25°C in water (estimated; for molecular formula C21H40O5) (EPISuite, 2017).

1.7.4. pKa

No data available to us at this time.

1.7.5. Flashpoint

CAS RN 73398-61-5: (°C): ca. 220 (open cup) (IUCLID, 2000) **CAS RN 65381-09-1:** (°C): 142.6±13.1 (estimated) (ChemSpider)

1.7.6. Flammability limits (vol/vol%)

No data available to us at this time.

1.7.7. (Auto)ignition temperature

(°C): No data available to us at this time.

1.7.8. Decomposition temperature

(°C): No data available to us at this time.

1.7.9. Stability

No data available to us at this time.

1.7.10. Vapor pressure

CAS RN 73398-61-5: 0.01 hPa at 20°C (IUCLID, 2000) **CAS RN 65381-09-1:** 0.0±2.5 mmHg at 25°C (estimated) (ChemSpider); 2.89E-008 mmHg at 25°C (estimated; for molecular formula C21H40O5) (EPISuite, 2017)

1.7.11. log Kow

CAS RN 73398-61-5: 3 at 23°C (IUCLID, 2000) **CAS RN 65381-09-1:** 6.23 (estimated; for molecular formula C21H40O5) (EPISuite, 2017); 6.90 (estimated) (ChemSpider)

2. General information

2.1. Exposure

Used as a solvent for colours and perfumes, an emollient, solvent, moisturizer, dispersant, solubiliser and suspending agent in cosmetics and pharmaceutricals, a plasticizer for fats, and as a lubricity vehicle, a food emulsifier, a bakery lubricant, a release agent, a glazing agent for confectionery, and a solvent carrier for flavours and fragrances (Ash and Ash, 2004).

INCI Name	CAPRYLIC/CAPRIC TRIGLYCERIDE
Description	Decanoic acid, ester with 1,2,3-propanetriol octanoate; Glycerides, mixed decanoyl and octanoyl
CAS #	73398-61-5 / 65381-09-1
EINECS/ELINCS #	277-452-2 / 265-724-3
Cosmetics Regulation provisions	
Functions	FRAGRANCE PERFUMING SKIN CONDITIONING
SCCS opinions	
Identified INGREDIENTS or substances e.g.	
INCI Name	CAPRYLIC/CAPRIC GLYCERIDES
Description	Glycerides, mixed decanoyl and octanoyl
CAS #	73398-61-5
EC #	277-452-2
Cosmetics Regulation provisions	
Functions	· SKIN CONDITIONING - EMOLLIENT · SKIN CONDITIONING - EMULSIFYING · SKIN CONDITIONING
SCCS opinions	

Identified INGREDIENTS or substances e.g.		

As taken from CosIng (Cosmetic substances and ingredients database). Available at https://ec.europa.eu/growth/tools-databases/cosing/, accessed January 2022.

Glycerides, mixed decanoyl and octanoyl (CAS RN 73398-61-5) are listed as fragrance ingredients on the US EPA InertFinder Database (2021) and, along with decanoic acid, ester with 1,2,3-propanetriol octanoate (CAS RN 65381-09-1) by the IFRA.

Caprylic/capric triglyceride 1 (CAS RN 65381-09-10) and caprylic/capric glycerides (CAS RN 73398-61-5) are listed as ingredients in personal care products (at 3-10% and 1-10%, respectively, where specified) by the CPID.

“Caprylic/Capric Triglyceride has the highest frequency of use; according to 2017 VCRP data, it is used in 6000 cosmetic formulations, with uses reported for all exposure types.”

“Use concentration survey data were collected in 2015/2016 (and updated in 2017) for some of ingredients, and in 2017 for the remaining ingredients. The results indicate that Triethylhexanoin has the highest maximum use concentration in leave-on formulations, with concentrations of 100% reported for face and neck formulations and 63% in lipstick formulations (Table 5). Caprylic/Capric Triglyceride has the next highest maximum use concentration in leave-ons, with concentrations of 95.6% in face and neck products.”

“The frequency and maximum concentrations of use for the majority of these ingredients has increased when compared to the previous review. The most remarkable increase is in the frequency of use of Caprylic/Capric Triglyceride; in 2003, this ingredient was reported to be used in 763 formulations and in 2017, it is reported to be used in 6000 formulations.”.

Caprylic/Capric Triglyceride, is a component of a homogenous lipid emulsion approved for intravenous (i.v.) infusions indicated for use in adults as a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.27 The lipid content of the infusion is 0.20 g/ml, and comprises a mixture of soybean oil, Caprylic/Capric Triglyceride, olive oil, and fish oil; recommended dosing is 1 to 2 g/kg/day, not exceeding 2.5 g/kg/day.

As taken from CIR, 2017

Caprylic/capric triglyceride (CAS RNs 65381-09-1 and 73398-61-5) is used as a anticaking agent, emulsifying agent, fragrance ingredient and, skin-conditioning agent – occlusive in non-medicinal natural health products (Health Canada, 2021).

2.2. Combustion products

No data available to us at this time.

2.3. Ingredient(s) from which it originates

“The ingredient is obtained by the hydrolysis of coconut oil or palm kernel oil followed by the fractionation and separation of the desired fatty acids which are esterified with glycerin to form acylglycerols” (FDA, Docket: Captrin 2005). As taken from http://www.fda.gov/ohrms/dockets/dockets/94g0237/94g-0237-sup0001-Tab-A-vol1.pdf

“Caprylic/Capric Triglyceride is manufactured by hydrolyzing coconut oil, removing the free glycerin, and separating the medium chain length fatty acids by fractional distillation.5 The acids are then blended in the proper ratio and re-esterified with glycerin.”

As taken from CIR, 2017

3. Status in legislation and other official guidance

As taken from FDA (2021) available at https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=FoodSubstances

Select Committee on GRAS Substances (SCOGS) Opinion: Caprylic Acid (21 CFR Section: 184.1025)

Caprylic acid, a naturally occuring constituent of many foods, is absorbed and metabolized by man. Triblycerides [sic] containing this fatty acid are hydrolyzed in the intestinal mucosa and the liberated fatty acids are transported in the portal ciculation and are almost completely oxidzed in the liver. Significant oxidation also appears to occur in the intestinal mucosa. Little caprylic acid is stored, and long-term feeding at high levels results in decreased overall fat storage that is indicative of nutritional utilization. thus caprylic acid is a fatty acid nutritionally utilizable by man and animals. Based upon consideration of the data presented in this report the Select Committee concludes that: There is no evidence in the available information on caprylic acid that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when it is used at levels that are now current or that might reasonably be expected in future.

As taken from SCOGS (FDA, 2015): Caprylic acid available at http://wayback.archive-it.org/7993/20171031063619/https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/SCOGS/ucm261239.htm

There is REACH dossier on glycerides, mixed decanoyl and octanoyl (CAS RN 73398-61-5) (ECHA, 2021a)

Decanoic acid, ester with 1,2,3-propanetriol octanoate (CAS RN 65381-09-1) is pre-registered under REACH (“envisaged registration deadline 30 November 2010”) (ECHA).

Glycerides, mixed decanoyl and octanoyl (CAS RN 73398-61-5) and decanoic acid, ester with 1,2,3-propanetriol octanoate (CAS RN 65381-09-1) are not classified for packaging and labelling under Regulation (EC) No. 1272/2008 (ECHA, 2021b).

Decanoic acid, ester with 1,2,3-propanetriol octanoate (CAS RN 65381-09-1) is listed in the US EPA InertFinder Database (2021) as approved for nonfood use pesticide products and glycerides, mixed decanoyl and octanoyl (CAS RN 73398-61-5) are approved for food, nonfood and fragrance use pesticide products. For food use they are included under 40 CFR section 180
Glycerides, mixed decanoyl and octanoyl CAS RN 73398-61-5) is regulated by 21 CFR 172.854: FOOD FOR HUMAN CONSUMPTION; FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION
(US EPA, 2021).

Glycerides, mixed decanoyl and octanoyl (CAS RN 73398-61-5) and glycerol octanoate decanoate (CAS RN 65381-09-1) are included on the US EPA Safer Chemical Ingredients List (US EPA, 2021).

Mixed decanoyl and octanoyl glycerides (CAS RN 73398-61-5) and glycerol octanoate decanoate (CAS RN 65381-09-1) are listed in the US EPA Toxic Substances Control Act (TSCA) inventory and also in the US EPA 2020 CDR list (Chemical Data Reporting Rule).
US EPA 2020 CDR List. US EPA TSCA inventory

Glycerides, mixed decanoyl and octanoyl (CAS RN 73398-61-5) and decanoic acid, ester with 1,2,3-propanetriol octanoate (CAS RN 65381-09-1) are included on the New Zealand Inventory of

Chemicals and may be used as single component chemicals under appropriate group standards (New Zealand EPA, 2006).

The CIR Expert Panel concluded that Caprylic/Capric Triglyceride is safe in cosmetics in the present practices of use and concentration described in the safety assessment.

As taken from CIR, 2017

Glycerides, mixed decanoyl and octanoyl (CAS RN 73398-61-5) and decanoic acid, ester with 1,2,3-propanetriol octanoate (CAS RN 65381-09-1) “pose no unreasonable risk to human health based on Tier I assessment under the NICNAS IMAP assessment framework” (AICIS, 2017).

4. Metabolism/Pharmacokinetics

4.1. Metabolism/metabolites

“Medium chain triglycerides (MCTs)-based diets have been shown to cause minor alterations in serum lipid profiles, and have occasionally yielded slower rates of weight gain relative to LCT-based diets. Experimental studies in both animals and man have shown that MCT- based diets do not cause significant toxicity, even when the diets have consisted of upwards of 5% MCTs. Studies in adults have indicated that MCT- based diets yield lower cholesterol levels relative to LCT-based diets; in addition, MCT-based diets produced smaller increases in plasma triglycerides. In low birth weight infants, MCTs have been shown to improve fat absorption in the absence of a significant change in body weight. The results of some of these nutritional studies can be attributed to the fact that: (1) MCTs are calorically less dense than LCTs; (2) the energy retention of MCT-based diets has been shown to be less than that of LCT-based diets; and (3) the thermic response to food (TRF) is greater after an MCT-based meal. None of the fore- going effects is considered clinically adverse. Animal and clinical studies have also shown that MCTs do not have a significant effect on the absorption of vitamins A, D or E. The potential effects of dietary MCTs on the absorption of minerals from the intestine have been examined in several studies. A randomized study with low-birth-weight infants investigated the effect of MCT on 25- hydroxy vitamin D serum levels as well as the absorption and retention of calcium and phosphorus. In this study, 20 infants received a high calcium- and vitamin D-containing formula that contained 50% of its fat as either MCT or LCT. All infants began oral feedings before 7 days of age by intermittent gavage, and feedings were advanced to a goal of 150 ml/kg/day. Blood samples were obtained within the initial 24 hr of the feedings, within 24 hr of reaching a feeding level of 140 ml/ kg/day, and at two additional time points after reaching the target consumption of 150 ml/kg/day. Serum data for 25-hydroxy vitamin D showed no significant differences between the two groups at any of the sampling periods. Approximately 1 wk after attaining full feeding volumes, a 96-hr 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 percent absorption or retention of calcium or phosphorus between the two groups (Huston et al., 1983).

The effect of MCT- and Long chain Triglyceride (LCT)-containing formulas on calcium, phosphorus and magnesium balances and plasma levels of 1,25-dihydroxy vitamin D was investigated with 28 very-low-birth weight infants. Infants were randomized before the introduction of oral feeding to receive either a pre-term formula in which 40% of the fat consisted of LCTs (MCT group; n = 15) or a formula with a similar total fat content but contained only 6% MCTs (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-hr balance studies were carried out within approximately 2 wk of achieving the target intake level, which involved an analysis of blood, stools and urine levels for Ca, P, Mg and 1,25-dihydroxy vitamin D. The absorption and retention of Ca and Mg were approximately 10± 20% higher in the MCT group. The retention of phosphorus was approximately 15% lower in the LCT group, possibly due to a compensating increased urinary

excretion of phosphate caused by the lower Ca absorption. There was no significant difference in the plasma levels of 1,25-dihydroxy vitamin D between the two groups (Sulkers et al., 1992).

Keyayoglou et al. (1973) concluded that MCT- based diets do not alter Ca absorption. This study involved 10 adult patients who were administered 10 mCi 47CaCl2 in water after an overnight fast. Total body retention of 47Ca was determined from total body counts at 3 hr and 7 days post-treatment, before and after a 4-wk treatment with a low-fat diet supplemented with 60 ml/day of an oily preparation of MCT (caprylic 23.2%, capric 59.4% and lauric 17.4%). The mean 7-day retention of 47Ca was not different before and after the MCT treatment.

The findings of a study carried out by Tantibhedhyangkul and Hashim (1978) contrasted with the findings of Huston et al. (1983). Their study involved 34 low-birth-weight infants who were divided into three groups that received formulas similar in nutrient value but differed with respect to the fat sources. Group one (control) received corn oil, oleo and coconut oil (39:41:20); group two (40% MCT) received MCT, corn oil and coconut oil (40:40:20) and group three (80% MCT) received MCT and corn oil (80:20). Formula feeding began within the first week of life and was continued throughout the hospital stay, which ranged from 28 to 60 days. Stool and urine samples were collected during the second week of life and during the final week of hospitalization, and were analysed for calcium and magnesium levels. The mean calcium absorption, expressed as a percent of dietary calcium, was significantly increased (approx. 50±100%) in both of the MCT groups relative to control; magnesium absorption was significantly increased (approx. 50%) in the 80% MCT group relative to control. There was no significant difference in urinary calcium excretion, expressed per unit of urinary creatinine, among the three groups. Urinary magnesium excretion was comparable between the control and MCT groups. Clinical trials have indicated that normal dietary levels of MCTs have no adverse effect on the absorption and retention of calcium, magnesium or phosphorus. In several studies, enhanced absorption and retention of these minerals occurred, but this is not considered to be clinically adverse. Most of these studies have been conducted on infants wherein MCTs supplied only a portion (50%) of the fat content of the diet. However, considering that infants have the largest consumption of fat on a body weight basis, the dietary levels of MCT in other population groups would also not be expected to have adverse effects on vitamin and mineral levels. Therefore, the reported increase in absorption of calcium, magnesium and phosphorus following MCT consumption remains inconclusive, but is not considered to be an adverse effect."

As taken from Traul KA et al. Food Chem Toxicol. 2000 Jan; 38(1):79-98. Science Direct, 2011 available at http://www.sciencedirect.com/

The hepatic mitochondrial metabolism of MCFAs such as caprylic and capric acid ultimately results in an excess of acetyl-CoA which in turn results in the production of acetate, CO2 and ketone bodies, with a minor portion serving to lengthen endogenous fatty acids (Bach and Babayan, 1982). However, some investigators have suggested that MCT diets, when fed in excess of caloric needs, might lead to increased de novo fatty acid synthesis and enhanced fatty acid elongation activity in the liver (Hill et al., 1990). The majority of the MCFAs are catabolized within the liver with only a minor portion reaching the general circulation bound to albumin.

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. Patients with liver cirrhosis do not utilize MCTs or their resulting fatty acid components as efficiently as healthy individuals, resulting in higher levels of circulating caprylic acid. Although very high circulating levels of caprylic acid can cause central nervous system toxicity (coma), these concentrations are not achieved from consuming MCTs, even at levels higher than would normally be found in food products (e.g. about 10–15% in baked goods .

"When absorbed from the digestive tract, Caprylic/Capric Triglyceride is hydrolyzed, and the fatty acids are catabolized to C2 fragments which may be further metabolized either to CO2 or to form long-chain fatty acids (Elder RL, 1980). Caprylic/Capric Triglyceride can undergo hydrolysis by

enzymatic or chemical means to produce free fatty acids, partial glycerides, and glycerin. The free fatty acids may, in turn, undergo enzymatic β-oxidation. β-Oxidation of caprylic acid forms β-ketocaprylic acid and can be further oxidized to yield acetic acid and C6,-acid."

"C > 12 are degraded by salivary, intestinal and pancreatic lipases into two fatty acids and a monoacyl glycerol, whereas, Caprylic/Capric Triglyceride is degraded by the same enzymes into three fatty acids and the simple glycerol backbone. Caprylic/Capric Triglyceride is readily absorbed from the small intestine directly into the bloodstream and transported to the liver for hepatic metabolism, while C > 12 are incorporated into chylomicrons and enter the lymphatic system. Caprylic/Capric Triglyceride is readily broken down to carbon dioxide and two-carbon fragments."

As taken from CIR, 2017

4.2. Absorption, distribution and excretion

"Medium chain triglycerides (MCTs) are partially hydrolysed by lingual lipase in the stomach and then rapidly and efficiently by pancreatic lipase within the intestinal lumen, thereby allowing for the direct absorption of medium-chain fatty acids (MCFAs) via the portal veito the liver rather than through the thoracic duct lymph system which is the conventional route for the absorption of triglycerides containing long-chain fatty acids. A minor fraction of MCFAs by-pass the liver and are distributed to peripheral tissues via the general circulation (Babayan, 1988;Bach and Babayan, 1982; Greenberger and Skillman, 1969). The MCFAs are catabolized predominantly in the liver to C2 fragments. The C2 fragments are further converted to CO2 or used to synthesize longer-chain fatty acids. Very little of the MCT, if any, is stored in adipose tissues (CTFA, 1980; Greenberger and Skillman, 1969). There are no published data available concerning absorption and metabolism of MCT following topical application. It has been reported, however, that if MCTs are subjected to high-pressure submicronization, they can provide an effective vehicle for drugs to be absorbed through the skin (Schwartz et al., 1995). Any portion of an applied dose that would be absorbed would probably be metabolized by the liver. The available information on the absorption and metabolism of MCTs suggests that MCTs injected into muscle could be absorbed into the blood stream and transported to the liver for metabolism and breakdown.

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

As taken from Traul KA et al. Food Chem Toxicol. 2000 Jan; 38(1):79-98. Science Direct, 2011 available at http://www.sciencedirect.com/

"Caprylic/Capric Triglyceride is readily absorbed from the small intestine directly into the bloodstream and transported to the liver for hepatic metabolism."

As taken from CIR, 2017

4.3. Interactions

Medium chain triglycerides (MCTs)-based diets have been shown to cause minor alterations in serum lipid profiles, and have occasionally yielded slower rates of weight gain relative to LCT-

based diets. Experimental studies in both animals and man have shown that MCT- based diets do not cause significant toxicity, even when the diets have consisted of upwards of 5% MCTs. Studies in adults have indicated that MCT- based diets yield lower cholesterol levels relative to LCT-based diets; in addition, MCT-based diets produced smaller increases in plasma triglycerides. In low birth weight infants, MCTs have been shown to improve fat absorption in the absence of a significant change in body weight. The results of some of these nutritional studies can be attributed to the fact that: (1) MCTs are calorically less dense than LCTs; (2) the energy retention of MCT-based diets has been shown to be less than that of LCT-based diets; and (3) the thermic response to food (TRF) is greater after an MCT-based meal. None of the fore- going effects is considered clinically adverse. Animal and clinical studies have also shown that MCTs do not have a significant effect on the absorption of vitamins A, D or E. The potential effects of dietary MCTs on the absorption of minerals from the intestine have been examined in several studies. A randomized study with low-birth-weight infants investigated the effect of MCT on 25- hydroxy vitamin D serum levels as well as the absorption and retention of calcium and phosphorus. In this study, 20 infants received a high calcium- and vitamin D-containing formula that contained 50% of its fat as either MCT or LCT. All infants began oral feedings before 7 days of age by intermittent gavage, and feedings were advanced to a goal of 150 ml/kg/day. Blood samples were obtained within the initial 24 hr of the feedings, within 24 hr of reaching a feeding level of 140 ml/ kg/day, and at two additional time points after reaching the target consumption of 150 ml/kg/day. Serum data for 25-hydroxy vitamin D showed no significant differences between the two groups at any of the sampling periods. Approximately 1 wk after attaining full feeding volumes, a 96-hr 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 percent absorption or retention of calcium or phosphorus between the two groups (Huston et al., 1983). The effect of MCT- and Long chain Triglyceride (LCT)-containing formulas on calcium, phosphorus and magnesium balances and plasma levels of 1,25-dihydroxy vitamin D was investigated with 28 very-low-birth weight infants. Infants were randomized before the introduction of oral feeding to receive either a pre-term formula in which 40% of the fat consisted of LCTs (MCT group; n = 15) or a formula with a similar total fat content but contained only 6% MCTs (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-hr balance studies were carried out within approximately 2 wk of achieving the target intake level, which involved an analysis of blood, stools and urine levels for Ca, P, Mg and 1,25-dihydroxy vitamin D. The absorption and retention of Ca and Mg were approximately 10± 20% higher in the MCT group. The retention of phosphorus was approximately 15% lower in the LCT group, possibly due to a compensating increased urinary excretion of phosphate caused by the lower Ca absorption. There was no significant difference in the plasma levels of 1,25-dihydroxy vitamin D between the two groups (Sulkers et al., 1992). Keyayoglou et al. (1973) concluded that MCT-based diets do not alter Ca absorption. This study involved 10 adult patients who were administered 10 mCi 47CaCl2 in water after an overnight fast. Total body retention of 47Ca was determined from total body counts at 3 hr and 7 days post-treatment, before and after a 4-wk treatment with a low-fat diet supplemented with 60 ml/day of an oily preparation of MCT (caprylic 23.2%, capric 59.4% and lauric 17.4%). The mean 7-day retention of 47Ca was not different before and after the MCT treatment. The findings of a study carried out by Tantibhedhyangkul and Hashim (1978) contrasted with the findings of Huston et al. (1983). Their study involved 34 low-birth-weight infants who were divided into three groups that received formulas similar in nutrient value but differed with respect to the fat sources. Group one (control) received corn oil, oleo and coconut oil (39:41:20); group two (40% MCT) received MCT, corn oil and coconut oil (40:40:20) and group three (80% MCT) received MCT and corn oil (80:20). Formula feeding began within the first week of life and was continued throughout the hospital stay, which ranged from 28 to 60 days. Stool and urine samples were collected during the second week of life and during the final week of hospitalization, and were analysed for calcium and magnesium levels. The mean calcium absorption, expressed as a percent of dietary calcium, was significantly increased (approx.

50±100%) in both of the MCT groups relative to control; magnesium absorption was significantly increased (approx. 50%) in the 80% MCT group relative to control. There was no significant difference in urinary calcium excretion, expressed per unit of urinary creatinine, among the three groups. Urinary magnesium excretion was comparable between the control and MCT groups. Clinical trials have indicated that normal dietary levels of MCTs have no adverse effect on the absorption and retention of calcium, magnesium or phosphorus. In several studies, enhanced absorption and retention of these minerals occurred, but this is not considered to be clinically adverse. Most of these studies have been conducted on infants wherein MCTs supplied only a portion (50%) of the fat content of the diet. However, considering that infants have the largest consumption of fat on a body weight basis, the dietary levels of MCT in other population groups would also not be expected to have adverse effects on vitamin and mineral levels. Therefore, the reported increase in absorption of calcium, magnesium and phosphorus following MCT consumption remains inconclusive, but is not considered to be an adverse effect.

As taken from Traul KA et al. Food Chem Toxicol. 2000 Jan; 38(1):79-98. Science Direct, 2011 available at http://www.sciencedirect.com/

“The present study sought to demonstrate the effect of dietary intake of medium-chain triacylglycerides (MCTs) on the intestinal absorption of a poorly permeable compound of intermediate molecular weight (FITC-dextran 4000 [FD-4]). As a model of MCTs, C8-C12 fatty acid triacylglyceride (COCONAD ML) was mainly used, and the dose strength of each triglyceride was set with consideration of the dietary ingestion dose (12.5 mg/rat). When FD-4 with MCTs dispersed in fasted state simulated intestinal fluid containing surfactants was administered into the rat jejunum, the intestinal absorption of FD-4 was significantly higher than when administered with a similar solution with or without corn oil (long-chain triglycerides). The effects of pretreatment by MCT lipolysis, inhibition of endogenous lipases, and different dose timings of MCTs and FD-4 on the intestinal absorption of FD-4 indicated that medium-chain fatty acids, such as caprylic acid and capric acid, released from MCTs by lipolysis in the small intestine significantly enhanced the intestinal absorption of FD-4, but the effect was transient. In addition, a similar effect was observed when MCTs were dispersed in soymilk, although large interindividual variation was detected. These findings suggested that dietary intake of MCTs might affect the intestinal absorption of poorly permeable compounds.” As taken from Kataoka M et al. 2020. Mol Pharm. 17(1), 212–218. PubMed, 2020 available at https://pubmed.ncbi.nlm.nih.gov/31756103/

5. Toxicity

5.1. Single dose toxicity

Acute oral toxicity

Type	LD50
Species	Rat
Value	>34000 mg/kg bw
GLP	no
Remark	Groups of 10 rats (Wistar, male) received 4.5, 9.0, 18.0 or 36.0 ml/kg of undiluted test substance per gavage; no animal died during the study; 10 days after dosing all animals were sacrificed and submitted to autopsy; no pathological changes were observed.
Source	Huels AG Marl

Type	LD50
Species	Rat
Value	>5000 mg/kg bw
GLP	No data
Remark	Test material produced no mortality in male and female rats; all animals showed no changes in appearance or behavior presented no abnormalities at necropsy 14 days after treatment; no further details reported.
Source	Huels AG Marl
Type	LD50
Species	mouse
Value	>23750 mg/kg bw
GLP	No
Remark	Groups of 10 female mice of Tyler's Original Strain each were dosed with undiluted test material par gavage (12.5, 20.0 or 25.0 ml/kg); lethargy, ataxia and dyspnea occurred within 15 minutes after dosing in the highest dosage group; 1 animal of the highest dosage group ad 2 animals of the mid dosage group died 24-28 hours after dosing; all symptoms disappeared in the survivors by the end of the third day.
Source	Huels AG Marl

Acute toxicity, other routes

Type	LD50
Species	mouse
Route of admin.	i.p.
Value	>23800 mg/kg bw
GLP	No
Remark	Animals were injected intraperitoneally with single doses of the test substance ranging from 1 to 24 ml/kg (1.0, 2.0, 4.0, 8.0, 16.0 or 24.0 ml/kg; 5 male rats/dose); all animals were sacrificed 14 days after dosing and submitted to autopsy; no death occurred during the study, no signs of toxicity or treatment related effects were observed.
Source	Huels AG Marl
Type	Acute i.v. toxicity
Remark	The acute toxicity by intravenous injection of emulsions of triglycerides of fatty acids (C2-C11) to mice was determined. Triglycerides were injected as 10% or 25% polyglycerol in glucose solution, containing phosphatides and polyglycerol mono-oleate; each type of emulsion was administered to

	at least 6 groups of 10 mice each. LD50 of C8-triglycerid: 3700 ± 194 mg/kg LD50 of C10-triglycerid: >10000 mg/kg
Source	Huels AG Marl
Type	Acute inhalation toxicity
Remark	10 male rats (Sprague-Dawley) and 10 guinea pigs (Birbright White/W 58) were exposed for six hours to an aerosol of the test substance at a concentration of 28.1 ug/l of air; the fraction with particles small enough to be inhaled into the lung (<5 um) represented 1.97 ug/l of air; three animals of each species were exposed to air and served as control. One hour after the exposure three animals and one control of each species were sacrificed for pathological examination, of the remaining animals were sacrificed 14 days after exposure; no death occurred throughout the study; observation during the exposure and 14 days thereafter revealed no symptoms, abnormal behavior of effects on body weight; no treatment related gross or microscopic defects were detected.
Source	Huels AG Marl

As taken from IUCLID Dataset (2000), Glycerides, mixed decanoyl and octanoyl (73398-61-5).

The acute oral toxicity of MCTs (caprylic/ capric triglyceride) has been evaluated in eight single dose studies in the mouse and the rat. In these studies doses between 4.5 ml/kg and 36 ml/kg did not produce mortality. The LD50 was not established, but is greater than 25 ml/kg (mice) or 36 ml/kg (rat). In a mouse study, Tyler's Original strain mice were treated with 5.0, 10.0, 20.0 and 25.0 ml/kg Miglyol 812 in a range-finding study with no deaths. In the definitive study conducted with 25 ml/kg, lethargy and ataxia occurred within 10 min after administration of 25 ml/kg, and dyspnoea was noted in some animals within 1 hr, but not thereafter. All animals appeared asymptomatic at the end of the first day. No necropsy observations were reported (Poole, 1977). Another mouse study tested Miglyol 810 (slightly higher portion of C8 fatty acids than Miglyol 812) at 12.5, 20.0 and 25.0 ml/kg. Transient ataxia, lethargy, dyspnoea and diuresis occurred within 15 min in the mid- and high-dose groups, and complete loss of activity was observed within 2 hr, followed by recovery, in several animals in the high dose group. Deaths occurred within 24 to 48 hr in two animals that received 20 ml/kg and one animal that received 25 ml MCT/kg. All symptoms disappeared in the survivors by the end of day 3. No necropsy observations were reported (Poole, 1977). Miglyol 812 was evaluated in fasted Wistar male rats, where a single dose from 4.5 to 36 ml/kg produced no toxic effect during the 10-day observation period or at necropsy. The only observation was that the animals receiving 18 and 36 ml/kg consumed less feed and excreted softer faeces for the first 2 days (Klimmer, 1971). In each of four single dose acute studies, five male and five female Wistar rats were given 5 g/kg Miglyol 812 and observed for 14 days. No deaths, adverse observations or abnormal gross pathology findings at necropsy were noted.

As taken from Traul KA et al. Food Chem Toxicol. 2000 Jan; 38(1):79-98. Science Direct, 2011 available at http://www.sciencedirect.com/

Acute inhalation toxicity

“Medium chain triglycerides (MCTs) was tested in an acute inhalation study with 10 male Sprague±Dawley rats and 10 male Pirbright White guinea pigs that were exposed to an aerosol of undiluted material for 6 hr. The nominal concentration of the Medium chain triglycerides (MCTs) (Miglyol 812) in the ex- posure chamber was 28.1 ml/litre air. The fraction of the aerosol with particles small enough to be inhaled (diameter E5 mm) was 1.97 ml per litre air. One control and three treated animals were sacrificed 1 hr after the exposure period. The remaining two control and seven treated animals of each species were sacrificed 14 days later. All animals were subjected to gross necropsy and microscopic examination of the respiratory tissues. In rats there were no abnormal general condition or behavioural observations, no differences in body weight or body

weight changes in treated animals when compared to the controls, nor any abnormal macroscopic findings in the lungs or trachea. Histopathological examination revealed two treated animals with frequencies of goblet cells of the bronchial mucosa which were very slightly increased over controls. Abnormal histological effects also included one control and two treated rats with very Toxicologic properties of MCTs 83 slightly increased levels of inflammatory infiltration of the stroma. This was described as a chronic, non-specific inflammation. These findings were considered to be insignificant because they were considered to be within the range of normal observations for that species and strain. No other gross or histopathological changes were noted (Reininghaus and RoÈ mer, 1977).

In guinea pigs, five treated animals exhibited an increase in goblet cells of the trachea. Small inflammatory, predominately peribronchial, foci were observed in the tracheas of seven treated and one control animal. Four treated guinea pigs exhibited hyperplasia of the basal cells and four animals exhibited squamous cell metaplasia. All obser-vations were ranked as very slight to insignificant because they were considered to be within the range of normal observations for that species and strain. The results of this study indicate that Miglyol 812 should be categorized as practically non-toxic by the inhalation route (Reininghaus and RoÈ mer, 1977).

In summary, while no recent acute toxicity studies were found, there is no reason to believe that newer data would affect the conclusion that MCTs and their component fatty acids have a very low acute toxicity in animals, regardless of the route of administration."

"Acute oral LD50 values for Caprylic/Capric Triglyceride were > 25 ml/kg in mice and >5 g/kg in rats (Elder RL, 1980). Male rats and guinea pigs in groups of ten each were exposed for 6 h in a 40 L chamber containing an aerosol of Caprylic/Capric Triglyceride at a nominal concentration of 28.1 µl/l of air. The fraction of the aerosol with particles small enough to be inhaled into the lung, i.e., with a diameter of 5 µm or less, represented 1.97 µl/l of the test substance. No adverse effects were observed."

As taken from CIR, 2017

"Acute oral toxicity studies were located for twelve (12) Glyceride Category members (CAS 61790-12-3 and 11099-07-3 (monoglycerides), 1323-39-3 and 65381-09-1 (diglycerides), 538-23-8, 7360-38-5, 85409-09-2, 73398-61-5, 8023-79-8, 67701-26-2 and 122-32-7 (triglycerides) and, 91744-20-6 (mixtures of mono-, di- and triglycerides)). The oral LD50s for rats are > 2000 mg/kg bw (CAS 122-32-7 (triglycerides) and 91744-20-6 (mixtures of mono-, di- and triglycerides)), and range up to > 48,000 mg/kg bw (CAS 7360-38-5 (triglyceride) (OECD 401, Directive 84/449/EEC, B.1, or no guideline specified)). At doses consistent with recent testing standards (i.e., 2000 to 5000 mg/kg bw), there were no clinical signs, changes in body weight or findings at gross necropsy. Similar findings (LD50s and lack of toxicity) were reported for mice. Acute aerosol inhalation studies were located for two glycerides (CAS 85409-09-2 and 73398-61-5, triglycerides); there were no adverse findings when rats or guinea pigs were exposed to 0.028 mg/L for six hours."

OECD Agreed Conclusions (2014) SIDS INITIAL ASSESSMENT PROFILE. Glycerides Category SIAP*5.2. Repeated dose toxicity*

5.2. Repeated dose toxicity

Species	Rat
Strain	Wistar
Route of admin.	Oral feed

Exposure period	3 months
Frequency of treatment	daily
Doses	10000 and 50000 ppm
Control group	Yes
GLP	No
Remark	20 male rats/dose; 20 male and 20 female rats/control; urine analysis and blood counts were done in the middle and at the end of the feeding period; serum GOT and GPT transaminases and free and esterified fatty acids were measured when the animals were sacrificed; no death occurred during the study; no treatment related effects on behavior, food intake, weight gain, relative organ weights or on histological findings were observed.
Source	Huels AG Marl
Species	Rat
Strain	Wistar
Route of admin.	Oral feed
Exposure period	47 weeks
Frequency of treatment	daily
Post. obs. period	none
Control group	Yes
GLP	No
Remark	Rats were fed a diet containing 19,6% of a triglyceride composed of 75% caprylic acid and 25% of capryc acid (MCT); controls were fed which differed only in the source of dietary fat (oleo oil, butter fat, coconut oil, corn oil); safflower oil was added to all diets containing MCT to insure adequacy of the essential fatty acids; the MCT containing diet supported normal growth and development, through growth rate was slightly less than that of rats fed the other diets; mortality was not markedly different between the groups; at autopsy, the carcass fat and smaller epididymal fat pads in the test group; histological study revealed no abnormalities in the intestine and liver.
Source	Huels AG Marl
Species	Rat

Strain	Wistar
Route of admin.	gavage
Exposure period	30 days
Frequency of treatment	Daily (7days/week)
Doses	1.0 r 3.0 ml/ rat
Control group	Yes
GLP	No
Remark	10 rats/dose or control group; the average doses were 7200 or 20200 mg/kg; weight gains of the treatment groups and the control group did not differ significantly; no signs of toxicity and no treatment related death was observed; animals of the lower dosage group showed no abnormal appearance or behavior and no urinary changes throughout the test; animals of the higher dosage group exhibited a decrease in appetite, fatty feces and a shaggy coat in the first five to seven days; all animals were submitted to autopsy at the end of the study and no showed pathological changes.
Source	Huels AG Marl

Type	Repeated doe toxicity study with chicken
Remark	A three week feeding study (16% of the test material in the diet) was conducted with 12 male chicken (White Leghorn), 12 male chicken served as control; the control and test diet were palatable to the animals, resulting in reduced feed consumption (control group-954g, test group-786 g) and reduced body weight gain for both groups; all mortalities (3 animals of the control group, 4 animals of the test group) seemed to reflect diet rejection and did not appear relted to the test material; gross autopsy did not reveal any abnormal liver and kidney changes.
Source	Huels AG Marl

As taken from IUCLID Dataset (2000), Glycerides, mixed decanoyl and octanoyl (73398-61-5).

3-week dietary toxicity study in chicks

“Miglyol 812 was incorporated into the diet at a level of 16% and fed to 12, 7-day-old Single Comb White Leghorn male chicks for 3 wk. A control group received standard diet. The treated group had reduced body weight gain, ruffled feathers and reduced muscle weight. These effects were due to the reduced feed consumption by chicks receiving the high fat diet. All mortality was due to starvation and not the consumption of Miglyol 812. The absence of “chick oedema factor” was determined by the absence of hydropericardium, hydroperitoneum and subcutaneous oedema at the time of autopsy. Very slight subcutaneous oedema was observed in three treated birds. Heart fluid volume was minimal in all chicks from treated and control birds and there was no evidence of an oedematous condition. Gross autopsy did not reveal any abnormal liver or kidney changes. The results of this study showed that Miglyol 812 did not contain chick oedema factor and that Miglyol is not toxic to chicks (Roth and Shapiro, 1981).”

30-day oral gavage toxicity study in rats

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

90-day parenteral toxicity study in rabbits

“In a 90-day trial, five rabbits were given 0.5 ml MCT (Miglyol 812) twice a week intramuscularly in the left and right thigh muscles. Two additional rabbits were used as control animals. Histological examination revealed small deposits of oil in the interstitial tissue of the muscle at the injection sites, generally in the form of oil cysts which were enclosed in a non-specific, fibre-rich granulation tissue. These responses were low grade and were considered to be late changes related to the oil cysts which were also described in acute study trials. Miglyol 812 was absorbed and metabolized without any physiological reaction, with the exception of the slight changes due to the initial depot at the injection site and to the injection itself. There were no indications of any changes in the brain, lungs, liver, kidney, spleen, myocardium or hilar lymph nodes. There were no effects on blood measurements of total lipids or total cholesterol when comparing values for the treated and control groups or for the measurements made at the start and end of the study. The results of the study show that Miglyol 812 has good parenteral compatibility in rabbits for both short-term or long-term use (Kracht, 1963b).”

3-month oral toxicity study in rats

“Groups of 20 male and 20 female rats were fed MCT (Miglyol 812) at 0, 10,000 or 50,000 ppm in the diet (representing 0, 1% and 5% of the diet) for 3 months. There were no reported signs of toxicity and no reported adverse effects on body weight, body weight gain, blood chemistry values or organ weights. The blood chemistry included measurements of liver enzymes AST and ALT, and non-esterified fatty acids and esterified fatty acids, which were all within the normal range. This study showed that feeding Miglyol 812 did not increase triglyceride levels or induce a hyperlipidaemic condition. 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 test material were not different from controls (Table 6). The no-observed-adverse-effect level (NOAEL) for this study was determined to be greater than 50,000 ppm in the diet (Klimmer O. (1971) Report on the toxicological testing on Miglyol 812 neutral oils. Unpublished Report of the Pharmacological Inst. of the Rhenish Friedrich-Wilhelm University. June 16Klimmer, 1971).”

3-month dietary toxicity study in rats

Groups of 25 male and 25 female weanling Crl:CD BR Sprague–Dawley rats were fed caprenin at 0, 5.23, 10.23 or 15.00% in the diet for 91 days. Caprenin is a mixed-chain MCT/LCT consisting of caprylic (23.2%), capric (26.6%) and behenic (C22, 45%) acids. Control animals were fed diets corn oil (12.1%) or a mixture of corn oil and Captex 300, an MCT (3.1% and 11.21%, respectively). All diets contained at least 3% corn oil to provide essential fatty acids and were balanced at about 4000 kcal/kg and provided 26.8% of dietary calories as fat, 19.4% as protein and 52.4% as carbohydrate.

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 on the corn oil/MCT diet. There were no significant differences in body weights or body weight gains across all groups. In the groups fed caprenin, male rats exhibited lower liver-to-body weight ratios and females exhibited lower absolute liver weights; both of these observations were attributed to reduced deposition of fat in the livers. Males on the 15.0% caprenin diet consumed significantly more feed and females consumed significantly less feed than the corn oil or corn oil/MCT dietary groups. Differences in haematologic and clinical chemistry values across all groups were considered to be not toxicologically significant,

approximating historical control values, and were not related to treatment. Necropsy evaluation included granular/pitted/rough renal observations for high-dose caprenin diet fed females; however, this observation had no histopathological correlate and was considered to be related to renal changes (nephrocalcinosis) that occur normally in female rats. There were no other gross or histopathological findings reported. There were no significant differences among groups in the total fat content, as weight percent, of the hearts, livers or perirenal fat pads; however, there was a trend to lower amounts of fat deposited in the livers of animals fed caprenin-containing diets. The NOAEL for caprenin was determined to be equal to or greater than 15% of the diet (13.2 and 14.6 gm/kg body weight/day for males and females, respectively) and for MCTs, in the corn oil/MCT diet, to be greater than 11.2% of the diet (approx. 9.2 gm/kg body weight/day) (Webb et al., 1993).

Subchronic dietary studies with MCTs and LCTs

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

Rat studies

No significant adverse effects were observed in a study wherein 15 male Sprague–Dawley rats were fed, via oral intubation, either an MCT- or LCT-containing diet which derived 50% of the calories from fat for 6 weeks. Animals fed the MCT diet had significantly lower levels of dissectable fat, which was attributed to higher resting and maximal norepinephrine-stimulated O2 consumption and metabolic rate. Liver fat and blood glucose values were comparable between the two groups (Baba et al., 1982).

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

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

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

As taken from Traul KA et al. Food Chem Toxicol. 2000 Jan; 38(1):79-98. Science Direct, 2011 available at http://www.sciencedirect.com/

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Human studies

A study was conducted with eight patients who were fed formula diets containing either MCTs [77.7% C8 (caprylic), 19.6% C10 (capric), 1.9% C6 and 0.8% C12], butter or corn oil as the sole isocaloric source of dietary fat. The study lasted up to 10 wk and used a crossover study design; each formula derived 40% of its caloric content from fat. The MCT- and corn oil-containing diets were shown to produce significantly lower cholesterol levels, relative to steady-state levels achieved on the butter diet. The only side-effect documented for the MCT formula was a transient period of nausea and abdominal fullness during the first 3–4 days (Hashim et al., 1960).

Four human volunteers who had fasted overnight were fed 1 g MCT/kg body weight (71% caprylic, 25% capric, 3% lauric). Their serum-free fatty acids showed a high proportion of octanoic acid and a low proportion of long-chain acids for 4 hr after feeding the MCT preparation. No toxicologic symptoms were reported (CTFA, 1980).

When 10 human volunteers ingested 100 ml (approx. 95 g) of synthetic fat (a triglyceride of 74% lauric, 17% capric, 5% caprylic, 3% myristic, and a trace of caproic), eight had no chylomicrons in their sera, and none developed diarrhoea or had fat in their faeces. All had increased levels of free fatty acids in their sera. These results support other data which show that MCTs are readily metabolized in the intestine and are absorbed primarily as free fatty acids without adverse effects (CTFA, 1980).

In another study, 10 non-obese males were overfed (150% of estimated energy requirements) two formula diets for 6 days each, in a randomized crossover design. The fat component of the diets represented 40% of caloric energy either as MCT or LCT. No significant clinical toxicity was reported. In contrast to the reports cited above, a reduction in fasting serum total cholesterol was noted for the LCT diet but not for the MCT diet. A threefold increase in fasting serum triglyceride values was noted for the MCT, but not for the LCT diet. It was suggested that MCT diets, when fed in excess of caloric needs, might lead to increased de novo fatty acid synthesis and enhanced fatty acid elongation activity in the liver (Hill et al., 1990).

In summary, the more recent subchronic studies provide confirmation of earlier dietary or parenteral treatment studies and the outcome of such studies appear to be consistent over time. The MCTs exhibit very low toxicity when administered in the diet at levels up to 15% of the diet. MCT-based diets have been shown to cause minor alterations in serum lipid profiles, which have occasionally translated into slower rates of weight gain relative to LCT-based diets. There is an apparent debate on the effect of an MCT-based diet on serum cholesterol levels. This appears to relate to the dietary comparisons being made. Compared to a high butterfat diet (Hashim et al., 1960), cholesterol levels were decreased, but compared to a high LCT diet (Hill et al., 1990), cholesterol levels were not decreased. None the less, the subchronic studies in both animals and man have indicated that MCT-based diets do not cause significant toxicity to humans or to laboratory animals.

As taken from Traul KA et al. Food Chem Toxicol. 2000 Jan; 38(1):79-98. Science Direct, 2011 available at http://www.sciencedirect.com/

“No signs of toxicity were observed in rabbits following 4 wks of applications of a tanning butter formulation containing 22% Caprylic/Capric Triglyceride at a dose of 2 g/kg, five times/wk for 4 wks, to intact and abraded skin (Elder RL, 1980). Two groups of 10 rats were dosed by gavage with 7.6 or 21.3 ml/kg undiluted Caprylic/Capric Triglyceride daily for 30 day (Elder RL, 1980). With the exception of a few gross observations made in the high-dose group in the first week of the study, no adverse effects were observed.”

“In 28-day gavage studies in Han-Wistar rats, dosing with 3.12 g/kg 33% Caprylic/Capric Triglyceride did not produce any signs of toxicity, (Healing G et al., 2016) but undiluted test material produced some gastrointestinal effects, decreased thymic weight, caused inflammation in the lungs, and resulted in changes in some clinical pathology parameters (Sellers RS et al., 2005). These changes were reversible. In Göttingen minipigs, clinical signs of toxicity were observed with 0.5 and 2 ml/kg/day Caprylic/Capric Triglyceride administered by gavage; no changes in organ weights or gross or microscopic lesions were observed (Le Bars G et al., 2015). In rats, a no-observed adverse effect level (NOAEL) of 10 mg/kg bw/day was reported in a 30 day study with Caprylic/Capric Triglyceride (ECHA).”

“Application of a perfumed skin softener formulation containing 4% Caprylic/Capric Triglyceride to the shaved skin of female rats at a dose of 2 ml/kg 5 days/wk for 13 wks did not produce any toxic effects (Elder RL, 1980). No toxic effects were noted in a 3-mos feeding study of 1 and 5% Caprylic/Capric Triglyceride in the diet of rats.”

“Three-month feeding studies were performed with Caprylic/Capric Triglyceride in rats (ECHA) and dogs (Matulka et al. 2009) The NOAELs were 5% and 15%, respectively, and no toxicologically-relevant signs of toxicity were observed at the highest doses.”

As taken from CIR, 2017

“Repeated dose oral (gavage or diet studies) have been located for six (6) of the Glyceride Category members (CAS 61790-12-3 (monoglyceride), 1323-39-3 and 65381-09-1 (diglycerides), 538-23-8, 85409-09-2 and 73398-61-5 (triglycerides). There were no adverse effects of treatment reported following repeated oral studies with rats, by either gavage or diet route. The NOAELs were =>2500 mg/kg bw, indicating the Glyceride Category members are not toxic. Although the studies do not conform to current, standard guidelines, the substances do not cause systemic toxicity. Similar results are expected for the Glyceride Category members that have not been tested.”

SIDS INITIAL ASSESSMENT PROFILE. Glycerides Category SIAP. OECD Agreed Conclusions (2014)

5.3. Reproduction toxicity

Type	Reproductive toxicity
Remark	In reproduction study young adult male and female rats (Mc Collum-Wisconsin Strain) were fed a diet containing 19.6% of a triglyceride of 75% caprylic and 25% capric acid for 3 weeks before mating; litter size and birth weight of the test animals were similar to those of rats on conventional or low fat diets, but mortality during lactation was somewhat higher and there was less weight gain due to a smaller volume of milk secreted; after weaning the F1 generation was fed as the F0 generation had been and showed a weight gain comparable of control rats on an oleo oil diet.
Source	Huels AG Marl

As taken from IUCLID Dataset (2000), Glycerides, mixed decanoyl and octanoyl (73398-61-5).

“In a study with Sherman albino rats that were fed diets containing 20% of either lard or MCT in addition to 0.09% linoleic acid for 10–12 months, no effect on fertility was noted. When treated male rats were mated at 9 months of age with control females, all males were found to be equally fertile and litters were normal with respect to number and weight. When female rats which had been maintained on the MCT diet supplemented with either 0.09 or 2.0% linoleic acid were mated with males that had been treated with the MCT diet+0.09% linoleic acid, normal litters occurred. However, the lactation performance of females on MCT diets supplemented with 0.09% linoleic acid was reported as being poor, as evidenced by lower survival and growth rates of their offspring. The second litter pups from females who had been maintained on the MCT+0.09% linoleic acid diet were then in turn 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. The second-generation animals initially showed signs of linoleic acid deficiency, but these symptoms eventually resolved without the addition of linoleic acid supplements. Thus, while dietary levels of linoleic acid affected offspring growth and survival parameters, the incorporation of 20% MCT had no adverse effects on reproduction (Kaunitz et al., 1958).

In a reproductive toxicity study, young adult male and female Wistar rats were fed a balanced diet containing 19.6% of an MCT of 75% caprylic and 25% capric acid for 3 wk before mating. This group was compared to concurrent groups fed high oleo oil, butter fat or coconut oil diets. Body weight gain and litter size and birth weights of the animals on the MCT diet were similar to those of rats on the other diets. Mortality of the F1 and F2 pups during lactation was somewhat higher, and weight gain was slightly lower in the MCT diet group pups. This was directly attributed to a smaller volume of milk secreted by the dams and was supported by observations that there was considerably less body fat on these animals. After weaning, the F1 and F2 generations, which continued to be fed the MCT diet, showed a weight gain comparable to that of control rats on the other diets. There were no adverse effects on reproductive parameters or on pup development aside from slightly lower body weight gains during the lactation period (Harkins and Sarett, 1968).

Two developmental toxicity studies were carried out, in parallel, with 25 pregnant female Crl:CD rats and 15 pregnant female HRa: (NZW) SPF rabbits administered a 3:1 mixture of MCT and LCT during the period of organogenesis. Test material administration was via intravenous infusion (tail vein in rats, ear vein in rabbits) of either 0, 1.0 or 4.28 g lipid/kg body weight/day. Female rats were sacrificed and necropsied on day 20 and female rabbits were sacrificed on day 29 of gestation. Ovaries were examined and the number of corpora lutea was recorded. The uteri were removed from each rat and weighed, and the number and placement of implantation sites (live and dead foetuses, and early and late resorptions) were recorded. Foetuses were removed, weighed and examined for external, soft tissue and skeletal abnormalities.

There were no test material-related deaths in either trial. There were no adverse effects of treatment in rats or rabbits administered 1.0 g lipid/kg body weight/day and there were no adverse effects of treatment on the foetal parameters.

Rats that received 4.28 g lipid/kg body weight/day exhibited a non-significant trend towards reduced feed consumption during treatment, tail lesions associated with extravasation of the test article, enlarged lymph nodes, spleens and renal pelvises and small thymuses. There were no statistically significant adverse effects on foetal parameters. The NOAEL for maternal toxicity in rats was equal to or greater than 4.28 g/kg body weight/day (3.21 g MCT/kg body weight/day) and the NOAEL for foetal toxicity and other foetal effects was equal to or greater than 4.28 g/kg body weight/day.

Rabbits that received 4.28 g/kg body weight/day exhibited statistically significantly reduced feed consumption, statistically significant body weight loss and faecal output during treatment. Enlarged lymph nodes, spleens and renal pelvises and small thymuses were also observed. Statistically significant effects observed in foetuses included foetal toxicity, evidenced by increased incidences of resorptions (post-implantation loss of 17.1% vs 2.3% in the controls), lower body weights (76%

of control values). Increased incidences of skeletal anomalies, including unossified skull bones, misaligned sternebrae, presacral vertebrae and fused ribs were noted, but were determined not to be statistically significant when compared to controls. These foetal effects were attributed to the dietary deprivation of the dams during the treatment period. The NOAELs for maternal toxicity and for foetal toxicity in rabbits were both greater than 1.0 g/kg body weight/day and less than 4.28 g/kg body weight/day (Henwood et al., 1997; Wilson et al., 1996).

An experiment was conducted to determine whether feeding MCTs to sows during late gestation (G) and early lactation (L) would improve neonatal pig survival. Beginning on day 91G and continuing through day 7L, sows were fed isoenergetic (7000 kcal metabolizable energy/day) and isonitrogenous (278 g crude protein/day) amounts of either control (19% starch, 2% soybean oil), long-chain triglycerides (LCT, soybean oil, 12%), or MCT (10% MCT, 2% soybean oil) diets. Sows (n=18, 19 and 17, respectively) were induced to farrow on day 112G. Litters were weighed at birth, before suckling, and on days 1, 3, 7 and 21L. There was no effect of treatment on average pig weight at any time and no difference in the number of live pigs at birth. Beginning on day 3L ($P<0.05$) and continuing through weaning (day 21L, $P<0.02$), survival was improved in litters from sows fed MCT relative to litters from sows fed the control diet. Overall survival rates were 80, 81 and 90% in control, LCT and MCT groups, respectively. The greatest improvement in survival was observed in pigs weighing less than 900 g at birth. Survival of pigs in this weight range was 32, 53 and 68% in control, LCT and MCT treatment groups, respectively. Although feeding MCT resulted in an increase in content of MCFAs in milk, these accounted for less than 5% of the fatty acids in milk and likely cannot account for the improved survival rate. The observation of increased blood glucose ($P<0.05$) at birth in pigs from both the LCT- and MCT-fed sows is supportive of a prenatal effect of the diets. The results suggest that not only is survival improved, but that certain reproductive parameters, such as litter size, live births, birth weights and litter survival during early lactation and late lactation, are not adversely affected by dietary administration of MCTs (Azain, 1993).

In summary, MCTs administered in the diet or by the intravenous route had no adverse effect on rat reproductive or developmental parameters. MCTs administered in the diet had no adverse effect on terminal gestational development and postnatal survival of pigs. In contrast, MCTs infused intravenously in rabbits over a daily 4-hr period at a level of 4.28 g/kg body weight caused a loss in body weight in dams and developmental toxicity in the pups from those dams. However, this effect may be attributed to dietary deprivation of the dams, especially in view of the absence of a similar effect in a parallel intravenous treatment study in rats. The newer studies affirm older data which show that MCTs are not reproductive or developmental toxicants."

As taken from Traul KA et al. Food Chem Toxicol. 2000 Jan; 38(1):79-98. Science Direct, 2011 available at http://www.sciencedirect.com/

There was no evidence that intravenous (iv) or dietary administration of MCTs adversely affected the reproductive performance of rats or resulted in maternal toxicity, foetal toxicity or teratogenic effects at doses up to 4.28 g/kg body weight/day (iv) or 12,500 mg/kg body weight/ day (dietary). There was no evidence that dietary administration of MCTs adversely affected the reproductive performance of pigs or resulted in maternal toxicity, foetal toxicity or teratogenic effects at doses up to 4000 mg/kg body weight/day in the diet. In rabbits, following iv administration, the maternal and foetal no-observed-adverse-effect levels (NOAELs) were between 1.0 and 4.28 g/kg body weight/ day.

As taken from Traul KA et al. Food Chem Toxicol. 2000 Jan; 38(1):79-98. Science Direct, 2011 available at http://www.sciencedirect.com/

"Effects on fertility and developmental toxicity studies were located for six (6) and five (5) Glyceride Category members, respectively. There were no effects on fertility (CAS 61790-12-3 (monoglyceride), 1323-39-3 and 65381-09-1 (diglycerides), 85409-09-2, 73398-61-5 and 8023-79-8 (triglycerides) or developmental effects (CAS 61790-12-3, monoglyceride, 538-23-8, 7360-38-5 and

8023-79-8, triglycerides) in rats, mice or hamsters in studies similar to OECD 416, FDA/WHO/DGHS safety evaluation protocol, 90 day studies examining reproductive organs, three–generation study or developmental studies with no protocol specified. In a developmental toxicity study in rats in which CAS 538-23-8 was used as the vehicle control (9500 mg/kg bw) and water was used as the negative control, it was evident that the vehicle itself exerted a mild degree of developmental toxicity. There was a statistically significant 8% increase in total soft tissue malformations in the vehicle control group compared to 0% in the water control group. Maternal weight gain and fetal size were also lower in animals receiving CAS 538-23-8 compared to the water controls, but these were not statistically significant." In a 3-generation study with CAS 73398-61-5 (triglyceride), during lactation the volume of milk secreted by rats receiving the medium chain triglyceride in the diet at 9800 mg/kg bw was smaller and resulted in slower gain in body weight; after weaning, normal growth of the rats resumed. In this study, the LOAEL for developmental toxicity was 9800 mg/kg bw. Although the studies do not all conform to current, standard guidelines, the NOAELs were all greater than 2000 mg/kg bw. Similar results are expected for the Glyceride Category members which have not been tested."

OECD Agreed Conclusions (2014) SIDS INITIAL ASSESSMENT PROFILE. Glycerides Category SIAP

5.4. Mutagenicity

In vitro genotoxicity

Type	Ames test
System of testing	Salmonella typhimurium TA97, TA98, TA100
Concentration	0-1000 ug/plate for all three strains
Metabolic activation	With and without
Result	negative
Remark	Only one test with three strains was performed; Solvent: DMSO Test was performed in presence and absence of liver S-9 of aroclor treated rats; the test substance did not induce mutation in this system.
Source	Huels AG Marl

As taken from IUCLID Dataset (2000), Glycerides, mixed decanoyl and octanoyl (73398-61-5).

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

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

In summary, the evidence for the genotoxicity of MCTs is weak. Tricaprylin was not classified as a carcinogen in the chronic carcinogenicity study and caprylic acid was not mutagenic in yeast or bacteria. The positive result with tricaprylin in one strain of bacteria in the Ames test, does not

appear to suggest that tricaprylin should be classified as a mutagen. Additional data in other in vitro or in vivo genotoxicity assays could confirm this assumption."

As taken from Traul KA et al. Food Chem Toxicol. 2000 Jan; 38(1):79-98. Science Direct, 2011 available at http://www.sciencedirect.com/

Genetic Toxicity 'in Vitro'

Type:	Ames test
System of testing:	Salmonella typhimurium
Concentration:	250, 500, 1000, 2000 and 4000 ug/plate
Metabolic activation:	with and without
Result:	negative
Method:	OECD Guide–line 471 "Genetic Toxicology: Salmonella thyphimurium Reverse Mutation Assay"
GLP:	yes
Test substance:	as prescribed by 1.1 – 1.4
Source:	Henkel KGaA Duesseldorf

As taken from IUCLID Dataset (2000), Caprylic/capric triglyceride (65381-09-1).

"A lipid emulsion that comprises a mixture of soybean oil, Caprylic/Capric Triglyceride, olive oil, and fish oil (test concentrations not provided) was not genotoxic in an Ames test, a chromosomal aberration assay, or a hypoxanthine phosphoribosyl transferase (HPRT) gene mutation assay (FDA, 2016). In vivo, the emulsion was not genotoxic in a bone marrow cytogenic study in rats."

As taken from CIR, 2017

5.5. Cytotoxicity

"The cytotoxic effects against human tumor cells and influence on the immune system of Medium chain triglycerides (MCTs), and Long chain Triglycerides (LCTs) and an MCT/LCT mixture were compared. MCTs showed more potent tumor cell cytotoxicity than did LCTs. Continuous exposure to MCTs also inhibited the cytotoxic effect of LAK cells much more strongly than did exposure to LCTs.

However, there is a discrepancy between the concentration of MCT, or the mixture, that could suppress the growth of tumor cells and the concentration that inhibited the cytotoxicity of LAK cells."

As taken from Traul KA et al. Food Chem Toxicol. 2000 Jan; 38(1):79-98. Science Direct, 2011 available at http://www.sciencedirect.com/

5.6. Carcinogenicity

"In a study in which Sherman albino rats were fed diets containing 20% of either lard or Medium chain triglycerides (MCTs) in addition to 0.09% linoleic acid for 10 to 12 months, no overt toxicity was observed and there was no difference in survival between the two groups. Rats fed MCT

gained approximately 15% less weight during the study. This difference was shown not to be the result of faecal fat losses. A second component of the study involved the comparison of serum cholesterol levels in rats fed the lard-based diet vs the MCT-based diet supplemented with either 0, 0.09 or 2% linoleic acid. Rats fed the MCT diet had serum cholesterol levels which ranged from 55 to 76 mg% vs 83 to 129 mg% for rat on the lard diet. The rats fed diets with 0.09% linoleic exhibited greater caloric requirements than the groups fed diets containing 2.0% linoleic acid or lard. There were no adverse toxicological effects reported for animals fed diets containing MCT (Kaunitz et al., 1958).

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

Toxicological properties of MCTs 91 The US National Toxicology Program (NTP) tested tricaprylin, a triglyceride in which all three fatty acids are C8, caprylic acid) in a 2-yr chronic toxicity and carcinogenicity study. In this study, male F344/N rats were gavaged with 0, 2.5, 5 or 10 ml tricaprylin/kg body weight daily, 5 days per week for 2 yr.

The 2-yr survival of high-dose tricaprylin male rats was lower than that of the control rats (0 ml/kgÐ31/50; 2.5 ml/kgÐ30/50; 5 ml/kgÐ31/50; 10 ml/kgÐ23/53) due to moribund kills and deaths that appeared to be related to toxicity. The mean body weight of the high-dose group was lower than that of the controls throughout the study, although the difference was less than 5% after wk 61. 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 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 leukaemia was decreased (23/50, 28/50, 22/50, 9/53). There were no significant increases in carcinomas found in this study.

Although the study report did not identify a toxicity NOAEL, it appears that there would not be a statistically significant difference in any of the observed parameters between untreated control and 2.5 ml/kg groups. Therefore, the toxicity NOAEL for tricaprylin would be 2.5 ml/kg body weight/day or about 2.37 g/kg body weight/day (NTP, 1994).”

“In contrast to the NTP study and to other chronic studies cited above, it has been suggested, in one report, that tricaprylin may act to facilitate tumour cell metastasis. In this study, rats were injected with ACL-15 tumour cells via the portal vein, then were placed on three sources of TPN. TPN consisted of tricaprylin as an MCT or soybean oil as an LCT or dextrose. These components comprised 50%, 50% and 100% of non-protein calories, respectively. Evaluation of liver surface metastases showed more surface metastases in rats that had been treated for 2 or 11 days with MCT following tumour cell inoculation (Ohkawa et al., 1997). This finding is difficult to interpret in view of the absence of increased incidences of tumours in the other studies cited, and in view of the fact that the livers of these rats were experimentally implanted with tumour cells. The e€ects of reduced calorie intake on the evolution of spontaneous tumours and on survival is the subject of

study by NTP and other laboratories (Dixit and Kacew, 1997; Giknis and Clifford, 1998; Hoberman et al., 1996; Kari and Abdo, 1997). Caloric restriction can be achieved, among other means, by reduction of dietary fat levels to less than 5%. It is established that doing so will result in increased survival and reduction of tumour incidences, especially endocrine-mediated tumours. The reverse phenomenon, of increased dietary calories/fat leading to increased spontaneous tumour incidences, has not been conclusively estab- lished. The capacity of tricaprylin to promote tumour metastases needs to be evaluated in other less invasive and more naturally occurring exper- imental scenarios. In summary, chronic studies in F344/N rats involving oral gavage of the MCT tricaprylin for 2 yr showed an increase in mortality at 10 ml/kg body weight/day (approx. 9.5 g/kg body weight/ day). This was accompanied by observations of increased incidences of pancreatic and forestomach hyperplasia and adenoma, but not carcinomas, at 5 and 10 ml/kg. In contrast, no significant toxic effects or effects on mortality were noted in Wistar rats or Sherman rats fed mixed-chain MCT in the diet for 1 yr at levels up to 20% of the diet (about 10 g/kg body weight/day). None of the e€ects seen in the subchronic studies suggests a carcinogenic potential for MCTs. Therefore, the results of the chronic studies are consistent with the ®ndings of the acute and subchronic studies and suggest that MCTs have very low toxicity. These studies also suggest that the route of administration (diet-ary inclusion vs oral gavage) may influence the apparent toxicity of MCTs during chronic administration."

As taken from Traul KA et al. Food Chem Toxicol. 2000 Jan; 38(1):79-98. Science Direct, 2011 available at http://www.sciencedirect.com/

5.7. Irritation/immunotoxicity

Skin irritation

Species	Rabbit
Result	Not irritating
Method	Other: EPA guidelines, (FIFRA, TSCA)
Remark	Irritation index: 0/8
Source	Huels AG Marl

Species	Rabbit
Result	Not irritating
GLP	no
Remark	3 male animals; the test substance was applied for 24, 48, and 72 hours; no irritating effects were observed
Source	Huels AG Marl

Species	Rabbit
Result	Not irritating
Method	Other: Performed by an official French method (Journal Official de la Republique Francaise)
Remark	Irritation index: 0,21/8

Source	Huels AG Marl

Species	Rabbit
Result	Not irritating
GLP	No data
Remark	Irritation index: 0/8 3 rabbits/sex, 0.5 ml of undiluted test material was applied to abraded and non-abraded skin, occluded patch; observation period: 24 and 72 hours after treatment; no further details reported
Source	Huels AG Marl

Species	Rabbit
Result	Not irritating
GLP	No data
Remark	Irritation index: 0.25/8 6 rabbits (sex unspec.) 0.5 ml of undiluted test material was applied to abraded and non-abraded skin, occluded patch; observation period: 24 and 72 hours after treatment; no further details reported
Source	Huels AG Marl

Species	Rabbit
Result	Not irritating
GLP	No data
Remark	Irritation index: 0.05/8 3 rabbits/sex, no further details reported
Source	Huels AG Marl

Species	Rabbit
Result	Not irritating
GLP	No
Remark	Irritation index: 0.92/8 6 rabbits (sex unspec.), no further details reported
Source	Huels AG Marl

Type: Biochemical or cellular interactions

Remark: The substance Decanoic acid, ester with 1,2,3–propanetriol octanoate was tested for comedogenity in the rabbit ear model. The substance was applied 50 % and 100 % twice a day for 5 days to the skin of the ears.

Result: no clinical signs of skin irritation. Histologically, no indication for a comedogenic effect was found. The substance is not comedogenic.

Source: Henkel KGaA Duesseldorf

As taken from IUCLID Dataset (2000), Caprylic/capric triglyceride (65381-09-1).

Eye irritation

Species	Rabbit
Result	Not irritating
Method	Other: EPA guidelines, (FIFRA, TSCA)
Remark	Irritation index: 2.04/110 (according to Draize) Cornea: x=0 Iris: x=0 Conjunctiva: -redness: x=0 - chemosis: x=0 The treated eye of one rabbit showed transient inflammation one hour after treatment; all treated eyes appeared normal 24 to 48 hours after treatment.
Source	Huels AG Marl

Species	Rabbit
Result	Not irritating
Method	Draize Test
GLP	No
Remark	No corneal nor iris damage was seen during the study; conjunctival irritation was very slight.
Source	Huels AG Marl

Species	Rabbit
Result	Not irritating
GLP	No
Remark	0.5 ml of the test substance were applied once daily to 3 male rabbits on 6 consecutive days; no irritating effects were observed.
Source	Huels AG Marl

Species	Rabbit
Result	Not irritating
Method	Other: Performed by an official French method (Journal Official de la Republique Francaise)
Remark	Irritation index: 2/110
Source	Huels AG Marl

Species	Rabbit
Result	Not irritating
Method	Draize Test

GLP	No data
Remark	Irritation index 0/110 6 rabbits, observation were made 24, 48 and 72 hours after treatment; no further details reported.
Source	Huels AG Marl
Species	Rabbit
Result	Not irritating
Method	Draize Test
GLP	No data
Remark	Irritation index 0/110 6 rabbits, observation were made 24, 48, 96 and 108 hours after treatment; no further details reported.
Source	Huels AG Marl
Species	Rabbit
Result	Not irritating
Method	Draize Test
GLP	No data
Remark	6 rabbits, observation were made 24, 48 and 72 hours after treatment; a very mild, transient conjunctival redness and discharge was reported, resulting in scores of 0.7/110 (24 hours) and 0.3/110 (48 and 96 hours); no further details reported.
Source	Huels AG Marl
Species	Rabbit
Result	Not irritating
Method	Draize Test
GLP	No
Remark	Irritation index: 0/110 6 rabbits, observation were made 24, 48 and 72 hours after treatment; no further details reported.
Source	Huels AG Marl

Sensitization

Type	Other: skin sensitisation
Species	Guinea pig
Result	Not sensitizing

Method	Draize Test
GLP	No
Remark	The test substance was applied as a 4% solution in ethanol to closely clipped areas on the backs and flanks every other day for 10 days; 24 hours after each application erythema and edema readings were zero in all cases; the challenge application was made 2 weeks after the last priming dose; 0/6 animals showed sensitization 24 hours after the challenge application.
Source	Huels AG Marl

As taken from IUCLID Dataset (2000), Glycerides, mixed decanoyl and octanoyl (73398-61-5).

Ocular irritation

“MCT solutions (10%, 20% and 50%) dissolved in paraffin liquid (DAB 6) were dropped into one eye of each of two human volunteers at 4- to 6-day intervals. An additional five male subjects were tested with undiluted material. No irritation reactions were observed (Potokar, 1971).

Six rabbit eye irritation studies have been conducted to determine whether administering MCT or caprylic/capric triglyceride to the eye causes irritation. In one study, instillation of 50 mm3 (0.05 ml) Miglyol 812 per day for 6 days to the conjunctival membrane of the eyes of three rabbits resulted in no inflammation of the membrane or changes in the cornea during the 10-day observation period (Klimmer, 1971). In five other ocular irritation studies, a single dose of 0.1 ml Miglyol 812 was administered to the eye and observations made for 1–14 days. In four of these studies the compound was considered to be non-irritating (Anonymous, 1977; Busimeier, 1975; Lewis and Palanker, 1977; Palanker, 1976a). In the fifth study (Palanker A. (1976b) Ocular and primary dermal irritation (rabbit), acute oral toxicity (rat). Unpublished Report of the Consumer Product Testing No 76101-1/3 (B-E 03848)Palanker, 1976b), very mild transient conjunctival redness and discharge of the eye in two of the six rabbits was observed. The test material in the latter study was 50% Miglyol 812 and 50% coconut oil.”

Dermal irritation

“In a dermal irritation study, 40 subjects were patch tested with undiluted MCT. Three readings were made and no skin irritation was noted (Ippen, 1970; Klimmer, 1971).

Dermal irritation capacity was evaluated after application of undiluted MCT (Miglyol 812) to the shaved skin on the backs of rabbits. Following 24, 48 or 72 hr of contact there was no evidence of irritation or inflammation (Klimmer, 1971). MCT was well tolerated in rabbits treated for 2 months in a repeated application cutaneous tolerance test. The test material was categorized as non-irritating (Guillot and Coquet, 1977). However, one sample tested was poorly tolerated and produced a primary irritation index (PII) score of 0.46. This sample caused vesicles to form in three animals, and two of the six biopsies showed pathological intra- and perifollicular retention type inflammation. In three separate tests of a 15% dilution of Miglyol 812 it was shown to be non-irritating (Guillot et al., 1977). Two other samples of MCT were determined to be mildly irritating to the skin when defined erythema and/or oedema was observed in five of six and six of six rabbits, respectively, 24 hr after treatment. The symptoms were not observed at 72 hr after treatment (Busimeier, 1975).”

“128 adult male and female human volunteers were tested with MCT using a modification of the Draize repeated insult patch test. All subjects had little or no irritation and none was sensitized. One subject had barely perceptible erythema at the first reading immediately following the removal of the first patch which had been applied for 48 hr (Henke and Ede, 1975).

12 women (age not stated) were tested with 0.4 ml MCT applied on a patch. New patches were applied daily to the same site for 21 consecutive days. They were removed 23 hr after application and read at 24 hr. One subject had an erythema score of 1.0 on a scale of 0 to 3 on day 16. The

investigators reported that all other scores were 0 and were ranked as negative. This MCT was considered essentially non-irritating for the amount used (Henke W. and Carabello F. (1975) Lanman test of cumulative irritant properties on a series of test materials. 5. Caprylic/capric triglyceride #0854 C. Hill Top Research Unpublished Report 75–414–70 #0854 (Miglyol 812)Henke and Carabello, 1975)."

"MCT was tested for potential phototoxic effects on the skin of human volunteers. Miglyol 812 was applied to the skin and then wiped off after 30 min. Immediately afterwards, the skin surface was divided by horizontal and vertical strips of adhesive plaster into fields approximately 1 cm2 in area. These fields were exposed to UV light (wavelength not specified) for graduated periods varying from 42 sec to 11.2 min. The skin was examined for changes, especially erythema, after 24 and 48 hr. Examination of the 20 patients noted no skin changes, especially an absence of erythema, after 24 and 48 hr of exposure to light for up to 11.2 min. It was concluded that Miglyol 812 has no phototoxic effect on human skin (Ippen H. (1980) Biological testing of Miglyol 812–neutral oil for phototoxic effects on human skin. Unpublished Report of the University Skin Clinic, Düsseldorf UniversityIppen, 1980).

In another study, 100 human patients who had previously displayed various allergic dermatoses, were tested by dermal application of a 1 cm2 patch of fabric that had been immersed in Miglyol 812. After 48 hr the skin test patches were removed and the treated surfaces were examined for the presence of simple erythema. No evidence of erythema (or other reactions) was noted, confirming that MCTs are unlikely to cross-react in patients with allergic dermatoses of other origin (Degos, 1968; Klimmer, 1971).

A sample of Miglyol 810 was applied to the skin of six guinea pigs as a 4% solution in ethanol with application every other day until 10 applications had been made. Challenge application followed 2 wk after the last induction application. 24 hr after each application readings were made of the erythema and oedema of any skin reactions. No irritation was observed following either the initiation or challenge applications. These results show that Miglyol 810 does not produce sensitization in the guinea pig when applied under these conditions (Anonymous, 1972).

In summary, the results of these studies support the position that MCTs are not dermal or eye irritants. MCTs also are not sensitizers and do not induce photosensitization. Further, these studies support the conclusion that MCTs are not toxic when administered by the dermal route."

"CASE REPORT

A 54-year-old non-atopic woman was referred with face eczema that had developed over the preceding 3 months. The patient had no personal history of interest. She reported severe pruritus after application of a new cosmetic cream for 5 months, MEL13 Advanced Melatonin Cream (PharmaMEL, Granada, Spain). Physical examination 508 NAVARRO-TRIVIÑO AND RUIZ-VILLAVERDE revealed an erythematous and edematous rash on the face (Figure 1A). A repeat open application test (ROAT) with MEL13 cream showed a positive skin reaction after 5 days (Figure 1B). Patch tests were performed with the European Comprehensive Baseline Series (Chemotechnique Diagnostics, Vellinge, Sweden), a cosmetic series (Chemotechnique Diagnostics), and the cream compounds supplied by the manufacturer. The results were interpreted according to the criteria of the International Contact Dermatitis Research Group. Patch tests were read on day (D) 2 and D4. The patient showed a positive patch test reaction to caprylic/capric triglyceride 1% pet. with an edge pattern (Figure 1C). Patch tests of 10 control patients showed no reaction. Allergic contact dermatitis caused by caprylic/capric triglyceride was diagnosed. Complete remission was observed after the MEL13 cream was avoided."

As taken from: Navarro-Triviño F. J. and Ruiz-Villaverde R. (2020) Allergic contact dermatitis caused by caprylic/capric triglyceride from an anti-aging cosmetic cream. Available at: https://pubmed.ncbi.nlm.nih.gov/32542693/

"CASE REPORT

A 21-year-old atopic woman was referred with a 6-month history of eyelid eczema, which had slowly progressed to involve the whole face (Figure 1). She was otherwise fit and well. Application of mild topical corticosteroids had not helped, but on stopping all cosmetics and over-the-counter face cream her dermatitis had settled completely. Patch testing was performed to the British Society for Cutaneous Allergy (BSCA) standard, medicament, and facial series, as well to the patient's own products. The patch tests were read, according to criteria of the International Contact Dermatitis Research Group, on day (D) 2 and D4 (no late readings were performed in accordance with our standard practice). There was one reaction only on D4 to one of the patient's own products, Aquaporin active revitalising eye cream (Beiersdorf, UK), tested undiluted. The patient recalled having started daily application of this eye cream a few months prior to the onset of the rash. Patch testing with the eye cream ingredients, kindly supplied by the manufacturer ready diluted for patch testing, revealed a single positive patch test reaction to caprylic/capric triglyceride (10% in pet.), negative on D2 and positive on D4 (2+). Further patch tests with caprylic/capric triglyceride (10% in pet.) in 10 consecutive control patients were negative. Patch test chambers used were Finn chambers (SmartPractice, Phoenix, Arizona) on Scanpor tape."

As taken From: Khan W. and Stone N. (2021). Facial allergic contact dermatitis caused by caprylic/capric triglyceride in a cosmetic cream. Available at: https://pubmed.ncbi.nlm.nih.gov/34862627/

Immune function

"Some investigators have pointed out that LCT emulsions may impair monocyte, lymphocyte and/or neutrophil functions. These changes seem, however, to be related to quantity and rate of lipid administration. It has been suggested also that emulsions containing predominantly MCTs have less of an adverse effect or no adverse effect at all.

Gogos, C., Kalfarentzos, F. and Zoumbos, N., 1990. Effect of different types of total parenteral nutrition on T-lymphocyte subpopulations and NK cells. American Journal of Clinical Nutrition 51, pp. 119–122 View Record in Scopus | Cited By in Scopus (51)Gogos et al. (1990) reported potential differences in the effects on the immune response based on comparisons made with LCT emulsions versus MCT/LCT mixtures. This study included 15 normal subjects, 20 patients receiving glucose-based total parenteral nutrition (TPN), 20 patients receiving LCT-based TPN and 20 patients receiving a 50:50 mixture of MCTs and LCTs. T-lymphocyte subpopulations, including total T cells and T-helper, T-suppressor and natural killer (NK) cells and the ratio of helper to suppressor T cells were determined before and 10 days after initiation of TPN. A significant decrease in the ratio of helper to suppressor T cells in the LCT group was found, although no such difference was detected in the MCT–LCT group. No difference was found in total T cells and helper, suppressor or NK cells.

A study was conducted to investigate the immunological effects of three TPN regimens in patients. In the first regimen, calories were derived solely from glucose. The other two were identical except that 50% of the calories were provided as an LCT lipid emulsion or as a 50:50 mixture of MCTs and LCTs. NK activity and lymphokine-activated killer (LAK) activity were significantly higher in patients receiving the MCT/LCT solution whereas significantly lower LAK activity occurred in patients receiving the LCT solution. Interleukin 2 content in activated T lymphocyte supernatants was significantly higher in patients receiving the LCT solution. It was suggested that TPN with LCT emulsions or with MCT containing emulsions perturb cytokine interactions; however, the effect is less with MCT containing emulsions and this may augment certain responses (Sedman et al., 1991).

Sedman et al. (1990) examined the effects of three lipid MCT- or LCT-based emulsions on IL- 2-related interactions in vitro. Mitogen-stimulated and IL-2 activated human lymphocyte proliferation were both inhibited in a dose-dependent manner in the presence of all three lipid emulsions. However, the effects were less marked with an emulsion in which half of the calories were derived from MCTs than with a similar emulsion made solely with LCTs. Similarly, the LCT emulsions

inhibited the generation of cytotoxic lymphokine-activated killer cells to a greater degree than did the MCT-containing solutions. Neither emulsion inhibited the proliferation of these cell lines, which are not growth-factor dependent, but did inhibit the growth of an IL-2-dependent cell line. They concluded that lipid emulsions can upset IL-2-dependent lymphocyte responses. These observations may have relevance for the tumour-bearing patient who is receiving TPN.

The cytotoxic effects against human tumour cells and influence on the immune system of MCTs, LCTs and an MCT/LCT mixture were compared. MCTs showed more potent tumour cell cytotoxicity than did LCTs. Continuous exposure to MCTs also inhibited the cytotoxic effect of LAK cells much more strongly than did exposure to LCTs. However, there is a discrepancy between the concentration of MCT, or the mixture, that could suppress the growth of tumour cells and the concentration that inhibited the cytotoxicity of LAK cells. Moreover, no damage was observed in peripheral blood lymphocytes or LAK cells or in their cytotoxicity when the cells were incubated with triglycerides for 2 hr/day. Thus, short-term contact with triglycerides could inhibit tumour growth while the immune system was maintained within normal range (Kimoto et al., 1998).

The data show, in general, that MCT emulsions may affect lymphokine interactions within the immune system, depending on the emulsion, the regimen and, most likely, the health status of the patient. Certain of these parameters appear to be less adversely affected by MCT emulsions than they are by LCT emulsions although the reasons are not understood at this time.

The toxic potential of MCTs for human bone marrow cells was evaluated in an in vitro test system. Bone marrow cells from healthy donors were exposed to emulsions of either LCTs or an MCT/LCT mixture for 24 hr, following which they were cultured for 14 days. Emulsion concentrations ranged from 0 to 10 mg/ml culture medium. Concentrations of 0.5 mg/ml or higher were reported to have significantly inhibited colony formation of the bone marrow cells, as compared to the controls. Effects were reported to be similar for LCTs and the MCT/LCT mixture except for erythroid burst-forming units, which were significantly more inhibited by the LCT emulsion (Beau et al., 1997). This study suggests that, for a tissue culture system, moderate to high levels of triglyceride emulsions can adversely affect primary bone marrow cell colonization. Without the metabolic capacity found in intact animals, these triglycerides would be free to affect cell membranes in the in vitro model, potentially altering membrane permeability. In the animal and human studies that have been conducted there have been no observations suggesting that triglycerides, including MCTs, have an adverse effects on bone marrow or marrow function.

Studies of the potential to affect the immune response suggest that, under conventional use, MCTs have no effect or may provide enhancement (e.g. IL-2, NK cell activity) to selective components of the immune system. Under extensive parenteral dosing situations, MCT emulsions may also down-regulate selected immune system functions such as LAK activity."

As taken from Traul KA et al. Food Chem Toxicol. 2000 Jan; 38(1):79-98. Science Direct, 2011 available at http://www.sciencedirect.com/

"Application of a perfumed skin softener formulation containing 4% Caprylic/Capric Triglyceride to the shaved skin of female rats at a dose of 2 ml/kg 5 days/wk for 13 wks did not result in any localized skin effects. Caprylic/Capric Triglyceride was not a sensitizer in guinea pigs. Undiluted Caprylic/Capric Triglyceride was not irritating when tested using groups of 12 (21-day patch test), or 40 (test methods not described), and it was not an irritant or sensitizer in 128, subjects (Draize repeated insult patch test)."

No irritation was observed in 4-h patch tests with undiluted Caprylic/Capric Triglyceride (ECHA).

"A facial oil containing 95.51% Caprylic/Capric Triglyceride was not an irritant is a 24-h single insult occlusive patch test in 17 human subjects (Anon, 2015) and it was not a sensitizer in a human modified maximization patch test with 26 subjects (Product Investigations Inc, 2015)."

"The photosensitization potential of a facial cream oil containing 95.51% Caprylic/Capric Triglyceride was evaluated in a RIPT photocontact allergenicity assay completed in 27 subjects

(KGL Inc. 2015) For induction, an occlusive patch consisting of 40 mg of the test material spread uniformly onto a 2 x 2 cm (10 mg/cm^2) cotton cloth was applied to the lower back of each subject for 24 h; immediately following patch removal, the test site was exposed to two minimal erythema doses (MEDs) from a xenon arc solar simulator. This procedure was repeated 2x/wk for 3 wks, for a total of 6 induction applications. The light source was a 150 W compact xenon arc solar simulator (Solar Light Company) equipped with a UV-reflecting dichroic mirror and a 1 mm thick Schott WG320 filter; a 1 mm thick UG11 filter was also used. The solar spectrum (SSR waveband) was used to determine the individual MED. The size of the irradiated field at skin level was approximately a 1cm diameter circle. Total irradiance at skin level was 90.0 mW/cm^2. The UVA intensity was 52.5 mW/cm^2.

Following a 10-day non-treatment period, a challenge patch was applied for 24 h to a previously untreated site on the opposite side of the back, followed by exposure to ½ MED of solar simulated radiation plus 4 J/cm^2 of UVA. (For the challenge, a 1 mm thick Schott WG-345 filter was added to eliminate the UVB component (290-320 nm) and to produce a continuous broadband UVA extending from 320 to 410nm.) An unirradiated site treated with the test product served as a "dark" control. The sites were examined at 48 and 72 hours after irradiation for evidence of photocontact sensitization. The facial oil containing 95.51% Caprylic/Capric Triglyceride did not possess a detectable photocontact-sensitizing potential in human skin."

"Caprylic/Capric Triglyceride was non-irritating, to at most very mildly irritating, to rabbit eyes (Elder RL, 1980)."

"Undiluted Triheptanoin (ECHA), Tristearin (ECHA), Caprylic/Capric Triglyceride (ECHA), and C8-12 Acid Triglyceride (ECHA), as well as Triisostearin at an unspecified concentration (ECHA), were not irritating in rabbit eyes."

As taken from CIR, 2017

5.8. All other relevant types of toxicity

Plasma creatine kinase activity was studied in rabbits 1, 3, 6, and 9 days after intramuscular (IM) injection of the vehicles, sunflower oil, olive oil, and caprylic/capric triglyceride (myritol; glyceryl tricaprylo-caprate). The vehicles did not increase plasma creatine kinase levels. This indicated that the vehicles may be used for IM drug administration without inducing tissue damage (Vinardell MP; Vives MA, 1996).

Immune function

Some investigators have pointed out that LCT emulsions may impair monocyte, lymphocyte and/ or neutrophil functions. These changes seem, however, to be related to quantity and rate of lipid administration. It has been suggested also that emulsions containing predominantly MCTs have less of an adverse effect or no adverse effect at all. Gogos et al. (1990) reported potential differences in the effects on the immune response based on comparisons made with LCT emulsions versus MCT/LCT mixtures. This study included 15 normal subjects, 20 patients receiving glucose-based total parenteral nutrition (TPN), 20 patients receiving LCT-based TPN and 20 patients receiving a 50:50 mixture of MCTs and LCTs. T-lymphocyte sub- populations, including total T cells and T-helper, T-suppressor and natural killer (NK) cells and the ratio of helper to suppressor T cells were determined before and 10 days after initiation of TPN. A significant decrease in the ratio of helper to suppressor T cells in the LCT group was found, although no such difference was detected in the MCT±LCT group. No difference was found in total T cells and helper, suppressor or NK cells. A study was conducted to investigate the immunological effects of three TPN regimens in patients. In the first regimen, calories were derived solely from glucose. The other two were identical except that 50% of the calories were provided as an LCT lipid emulsion or as a 50:50 mixture of MCTs and LCTs. NK activity and lymphokine-activated killer (LAK) activity were significantly higher in patients receiving the MCT/LCT solution whereas significantly lower LAK

activity occurred in patients receiving the LCT solution. Interleukin 2 content in activated T lymphocyte supernatants was significantly higher in patients receiving the LCT solution. It was suggested that TPN with LCT emulsions or with MCT containing emulsions perturb cytokine interactions; however, the effect is less with MCT containing emulsions and this may augment certain responses (Sedman et al., 1991). Sedman et al. (1990) examined the effects of three lipid MCT- or LCT-based emulsions on IL- 2-related interactions in vitro. Mitogen-stimulated and IL-2 activated human lymphocyte proliferation were both inhibited in a dose-dependent manner in the presence of all three lipid emulsions. However, the effects were less marked with an emulsion in which half of the calories were derived from MCTs than with a similar emulsion made solely with LCTs. Similarly, the LCT emulsions inhibited the generation of cytotoxic lymphokine-activated killer cells to a greater degree than did the MCT-containing solutions. Neither emulsion inhibited the proliferation of these cell lines, which are not growth-factor dependent, but did inhibit the growth of an IL-2-dependent cell line. They concluded that lipid emulsions can upset IL-2-dependent lymphocyte responses. These observations may have relevance for the tumour-bearing patient who is receiving TPN.

As taken from Traul KA et al. Food Chem Toxicol. 2000 Jan; 38(1):79-98. Science Direct, 2011 available at http://www.sciencedirect.com/

Type:	other: Phototoxicity
Remark:	Phototoxic properties were tested on hairless mice with 50 %substance.
Result:	There were no phototoxic properties found.
Type:	other: Phototoxicity
Remark:	Phototoxicity with hairless mice with 50 % Test substance.
Result:	Result: negative
Source:	Henkel KGaA Duesseldorf

As taken from IUCLID Dataset (2000), Caprylic/capric triglyceride (65381-09-1).

6. Functional effects on

6.1. Broncho/pulmonary system

“In 28-day gavage studies in Han-Wistar rats, dosing with 3.12 g/kg 33% Caprylic/Capric Triglyceride did not produce any signs of toxicity, (Healing G et al., 2016) but undiluted test material produced some gastrointestinal effects, decreased thymic weight, caused inflammation in the lungs, and resulted in changes in some clinical pathology parameters (Sellers RS et al., 2005). These changes were reversible.”

As taken from CIR, 2017

6.2. Cardiovascular system

No data available to us at this time.

6.3. Nervous system

“Animal studies have been carried out to investigate the potential CNS effects of the administration of high doses of caprylic acid.

The intraperitoneal administration of caprylic acid can induce coma in mice. At a dose of 15 µmol/g (2160 mg/kg), mice exhibited a transient period of drowsiness followed by coma. The mechanism underlying the resulting coma was shown to be the result of a selective effect on energy metabolism within cells of the reticular formation. These changes consisted of a decrease in ATP and phosphocreatine and an elevation of glucose and glycogen (McCandless, 1985).

MCTs can also cause CNS toxicity after intravenous administration in dogs. A study was carried out in dogs that were infused with trioctanoin (caprylic acid), after a 12-hr fast, at rates which increased in a stepwise fashion from 26 to 35 to 44 µmol/kg/min, with each infusion lasting for 80 min. These doses correspond to total doses of 1.15, 1.55 and 1.95 g/kg, respectively. No signs of toxicity were noted at the lowest infusion rate, but at the two higher rates hypotonia and somnolence were noted, followed by unconsciousness and repeated emesis in some animals. The infusion resulted in plasma concentrations of ketone bodies of 423, 756 and 859 nmol/ml at 80, 160 and 240 min; basal levels were 102 nmol/ml. These changes were accompanied by increases in plasma lactate, as well as electroencephalographic changes. Plasma octanoate concentrations ranged from 250 to 1500 nmol/ml (Miles et al., 1991).

In rats, mice, dogs, guinea pigs and monkeys, CNS effects require blood concentrations of octanoate of approximately 3–8 µmol/ml (Johnson and Cotter, 1986). The effect of intravenous sodium octanoate in rhesus monkeys was investigated. Infusions at doses of 5 m /kg for 20 min produced a clinical and electroencephalographic syndrome comparable to hepatic encephalopathy. The serum concentrations of sodium octanoate that were achieved in this experiment were described as many times higher than those observed in comatose cirrhotic patients which are in the range of 10 to 18 µEq/litre (10–18 nmol/ml) (Rabinowitz et al., 1978).

In summary, MCTs are catabolized and absorbed more efficiently than LCTs. In patients with cirrhosis of the liver, MCTs are capable of providing a significant source of calories. Cirrhosis-induced hepatic dysfunction also results in a decrease in the hepatic clearance of caprylic acid, which can lead to elevated levels of caprylic acid in the serum and in the spinal fluid. It is not known whether this is a causative factor in hepatic encephalopathy. Unesterified caprylic acid is capable of producing CNS toxicity in animal models comparable to that of clinical hepatic encephalopathy, but this was only achieved at serum caprylic acid concentrations 166- to 800-fold higher than those observed in patients with hepatic encephalopathy. In these studies the intravenous or intraperitoneal routes of administration are unrelated to the likely oral route of exposure in cirrhotic persons. Therefore, it is unlikely that high circulating levels of caprylic acid alone are responsible for the development of hepatic encephalopathy in cirrhosis patients. It also appears highly unlikely that the consumption of MCTs in the diet would pose any concern for neurological effects as a result of the metabolic release of caprylic acid."

As taken from Traul KA et al. Food Chem Toxicol. 2000 Jan; 38(1):79-98. Science Direct, 2011 available at http://www.sciencedirect.com/

6.4. Other organ systems, dependent on the properties of the substance

Regulation of adipogenesis by medium-chain fatty acids in the absence of hormonal cocktail (Abstract). We report here that octanoate and decanoate, 8-carbon and 10-carbon medium-chain fatty acids (MCFA), decreased adipogenesis in 3T3-L1 preadipocytes when treated with standard hormonal cocktail, but increased adipogenesis in a dose-dependent manner (with decanoate being more effective) when treated with basal media. Addition of dexamethasone to basal medium with either octanoate or decanoate further increased adipogenesis. In order to understand the adipogenic effects of MCFA in the absence of standard hormonal cocktail, postconfluent 3T3-L1 preadipocytes were treated with octanoate or decanoate, and the change in the expression of several adipogenic transcription factors and enzymes was investigated using real-time RT-PCR. Octanoate and decanoate up-regulated the mRNA expression of peroxisome-proliferator-activated receptor (PPAR) gamma, CCAAT/enhancer-binding protein (C/EBP) alpha,

fatty-acid-binding protein, sterol-regulatory element binding protein 1c, lipoprotein lipase and hormone-sensitive lipase, and the protein expression of PPARgamma and C/EBPalpha, with decanoate being more effective. Moreover, the PPARgamma antagonist GW9662 inhibited MCFA-induced lipid accumulation by about 50%. Decanoate and octanoate, to a lesser degree, increased lipid accumulation, which was associated with an increase in glycerol-3-phosphate dehydrogenase activity. These results show that octanoate and decanoate may stimulate differentiation of preadipocytes, at least in part, by their influence on the expression of PPARgamma and other adipocyte-specific factors. As taken from Yang JY et al. J Nutr Biochem. 2009 Jul; 20(7):537-43. PubMed, 2011 available at http://www.ncbi.nlm.nih.gov/pubmed/18789670

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

A subsequent study (Linscheer et al., 1970), in which control and cirrhotic patients were administered a test meal of MCTs (0.5 g per kg lean body mass), also showed that serum concentrations of caprylic acid were approximately twofold higher in the cirrhotic group. Furthermore, it was shown that caprylic acid concentrations were four- to fivefold higher in the spinal fluid of cirrhotic patients.

As described above, MCTs are absorbed and transported directly to the liver, where they are metabolized; thus, only a small fraction of free MCFAs reach the general circulation in the presence of normal hepatic function. In the presence of liver disease such as cirrhosis, the capacity of the liver can be significantly compromised, resulting in decreased clearance of caprylic acid in addition to a decreased production of albumin (Bach and Babayan, 1982). Although it has been demonstrated that cirrhotic patients have elevated blood and spinal fluid levels of caprylic acid following MCT ingestion (Linscheer et al., 1966 and Linscheer, W., Blum, A. and Platt, R., 1970. Transfer of medium chain fatty acids from blood to spinal fluid in patients with cirrhosis. Gastroenterology 58, pp. 509–515 View Record in Scopus | Cited By in Scopus (7)Linscheer et al., 1970), it has not been demonstrated that this is a causative factor in CNS effects described as hepatic encephalopathy (Johnson and Cotter, 1986; McCandless, 1985).”

As taken from Traul KA et al. Food Chem Toxicol. 2000 Jan; 38(1):79-98. Science Direct, 2011 available at http://www.sciencedirect.com/

“In 28-day gavage studies in Han-Wistar rats, dosing with 3.12 g/kg 33% Caprylic/Capric Triglyceride did not produce any signs of toxicity, (Healing G et al., 2016) but undiluted test material produced some gastrointestinal effects, decreased thymic weight, caused inflammation in the lungs, and resulted in changes in some clinical pathology parameters (Sellers RS et al., 2005). These changes were reversible.”

As taken from CIR, 2017

7. Addiction

JTI is not aware of any information that demonstrates that this ingredient has any addictive effect.

8. Burnt ingredient toxicity

Tobacco smoke condensates from cigarettes containing Glycerides, mixed decanoyl and ocanoyland an additive free, reference cigarettes were tested in a battery of in vitro and/or in vivo test(s). Within the sensitivity and specificity of the bioassay(s) the activity of the condensate was not changed by the addition of Glycerides, mixed decanoyl and ocanoyl. Table below provides tested level(s) and specific endpoint(s)

Endpoint	Tested level (ppm)	Reference
Smoke chemistry	200	JTI KB Study Report(s)
In vitro genotoxicity	200	JTI KB Study Report(s)
In vitro cytotoxicity	200	JTI KB Study Report(s)
Inhalation study	200	JTI KB Study Report(s)
In vivo genotoxicity	200	JTI KB Study Report(s)

9. Heated/vapor emissions toxicity

Aerosol from an electronic nicotine delivery system (ENDS) product that creates a vapor by heating an e-liquid; the vapor then passes through a capsule containing tobacco granules, containing Caprylic-capric triglycerides was tested in a battery of in vitro and/or in vivo test(s). Under the test conditions and within the sensitivity and specificity of the bioassay(s), no mutagenic, genotoxic or cytotoxic responses were observed when exposed to Aerosol Collected Matter (ACM) and/or aerosol Gas Vapor Phase (GVP) and no adverse findings from a 90-day in vivo repeat-dose inhalation toxicity study were observed after exposure to the aerosol even when exposure concentrations were the maximal amount that could be achieved with the specific product(s). These results are in contrast to those observed with combustible cigarette which showed mutagenic, genotoxic, cytotoxic and adverse effects upon exposure. The table below provides tested level(s) and specific endpoint(s):

Endpoint	Tested level	Reference
Aerosol chemistry	4.1082 mg/(tobacco portion; 310 mg)	Logic (2019)
In vitro genotoxicity	4.1082 mg/(tobacco portion; 310 mg)	Logic (2019)
In vitro cytotoxicity	4.1082 mg/(tobacco portion; 310 mg)	Logic (2019)
In vivo genotoxicity	4.1082 mg/(tobacco portion; 310 mg)	Logic (2019)
Inhalation study	4.1082 mg/(tobacco portion; 310 mg)	Logic (2019)

10. Ecotoxicity

10.1. Environmental fate

EPISuite provides the following data for CAS RN 73398-61-5:

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:

	Bond Method :	3.39E-010 atm-m3/mole (3.44E-005 Pa-	

	m3/mole)
Group Method:	6.74E-013 atm-m3/mole (6.83E-008 Pa-m3/mole)
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:	HLC: 2.743E-010 atm-m3/mole (2.779E-005 Pa-m3/mole) VP: 7.48E-011 mm Hg (source: MPBPVP) WS: 0.134 mg/L (source: WSKOWWIN)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]: Log Kow used:	5.29 (KowWin est)
Log Kaw used:	-7.858 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate):	13.148
Log Koa (experimental database):	None
Probability of Rapid Biodegradation (BIOWIN v4.10): Biowin1 (Linear Model): Biowin2 (Non-Linear Model) : Biowin3 (Ultimate Survey Model): Biowin4 (Primary Survey Model) : Biowin5 (MITI Linear Model) : Biowin6 (MITI Non-Linear Model): Biowin7 (Anaerobic Linear Model):	0.9304 0.9861 3.4196 (days-weeks) 4.3236 (hours-days) 0.9554 0.9411 0.3057
Ready Biodegradability Prediction:	YES

Hydrocarbon Biodegradation (BioHCwin v1.01): Structure incompatible with current estimation method!

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]: Vapor pressure (liquid/subcooled):	3.07E-007 Pa (2.3E-009 mm Hg)
Log Koa (Koawin est):	13.148
Kp (particle/gas partition coef. (m3/ug)): Mackay model: Octanol/air (Koa) model:	 9.78 3.45

Fraction sorbed to airborne particulates (phi): Junge-Pankow model:	0.997
Mackay model:	0.999
Octanol/air (Koa) model:	0.996

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:

Hydroxyl Radicals Reaction:

OVERALL OH Rate Constant =	88.8757 E-12 cm3/molecule-sec
Half-Life =	0.120 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life =	1.444 Hrs
Ozone Reaction:	No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi): 0.998 (Junge-Pankow, Mackay avg) 0.996 (Koa method) Note: the sorbed fraction may be resistant to atmospheric oxidation	
Soil Adsorption Coefficient (KOCWIN v2.00): Koc :	229.9 L/kg (MCI method)
Log Koc:	2.362 (MCI method)
Koc :	744.9 L/kg (Kow method)
Log Koc:	2.872 (Kow method)
Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]: Total Kb for pH > 8 at 25 deg C:	2.848E-002 L/mol-sec
Kb Half-Life at pH 8:	281.632 days
Kb Half-Life at pH 7:	7.711 years

(Total Kb applies only to esters, carbmates, alkyl halides)

Volatilization from Water:

Henry LC: 3.39E-010 atm-m3/mole (estimated by Bond SAR Method)

Half-Life from Model River:	3.343E+006 hours (1.393E+005 days)
Half-Life from Model Lake:	3.646E+007 hours (1.519E+006 days)
Removal In Wastewater Treatment: Total removal:	84.99 percent
Total biodegradation:	0.73 percent
Total sludge adsorption:	84.26 percent

Total to Air:	0.00 percent

(using 10000 hr Bio P,A,S)

Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.37	2.89	1000
Water	26.4	208	1000
Soil	73	416	1000
Sediment	0.222	1.87e+003	0

Persistence Time: 304 hr

The Ecological Categorization Results from the Canadian Domestic Substances List simply state that glycerides, mixed decanoyl and octanoyl (CAS RN 73398-61-5) and decanoic acid, ester with 1,2,3-propanetriol octanoate (CAS RN 65381-09-1) are not persistent in the environment.

Data accessed March 2017 on the OECD website: http://webnet.oecd.org/CCRWeb/Search.aspx

Biodegradation

Type: aerobic

Inoculum: other: sewage treatment plant effluent/biological stage

Concentration: 2 mg/l

Degradation: 88 – 73 % after 30 day

Result: readily biodegradable

Method: Directive 84/449/EEC, C.6 "Biotic degradation – closed bottle test"

Test substance: as prescribed by 1.1 – 1.4

Method: EG–RiLi 84/449 Anh.V C4–E

Test condition: #1: 2 mg/l referring to Active Substance: 88% with parameter % BSB/CSB

#2: 5 mg/l referring to Active Substance: 73% with parameter % BSB/CSB

Test substance: Active Matter = 100 %

Inoculum: activated sludge, domestic

Concentration: 100 mg/l

Degradation: 100 % after 28 day

Result: other: well biodegradable

Method: ISO Draft "BOD Test for insoluble substances"

Method: two phase closed bottle test

Source: Henkel KGaA Duesseldorf

Test condition: #1: 100 mg/l referring to Chemical oxygen demand: 100% with parameter % BSB/CSB

Concentration: 50 mg/l

Degradation: 93 – 94 % after 30 day

Method: other: RDA–Test according to Blok (AWU)

Remark: AWU–Test !

Test condition: #1: 50 mg/l referring to Chemical oxygen demand: 93% with parameter % BSB/CSB; #2: 50 mg/l referring to Chemical oxygen demand: 94% with parameter

Test substance: active Matter = 100 %

Type: anaerobic

Inoculum: anaerobic sludge

Degradation: 96.5 % after 57 day

Method: ECETOC Anaerobic biodegradation

Test condition: #1: 50 mg/l referring to Active Substance: 96.5% +–14% with parameter % Faulgasbildung

As taken from IUCLID Dataset (2000), Caprylic/capric triglyceride (65381-09-1).

10.2. Aquatic toxicity

Acute/Prolonged Toxicity to Fish

Type	Semistatic
Species	Brachydanio rerio (Fish, fresh water)
Exposure period	96 hour(s)
Unit	mg/l
Analytical monitoring	Yes
LC0	≥53
Method	Other: Directive 92/69/EEC, C.1
Year	1992
GLP	yes
Remarks	No toxic effects were observed below the water solubility (under test conditions)
Source	Huels AG Marl
Test substance	MIGLYOL 812

Type	Static
Species	Leuciscus idus (Fish, fresh water)
Exposure period	48 hour(s)

Unit	mg/l
Analytical monitoring	No
LC0	≥1000
Method	Other: Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fischr, DIN38412 Teil 15
GLP	no
Remarks	An emulsifier (MARLOWET EF) was added
Source	Huels AG Marl

Acute Toxicity to Aquatic Invertebrates

Species	Daphnia magna (Crustacea)
Exposure period	24 hour(s)
Unit	mg/l
Analytical monitoring	No
EC0	≥2.2
EC50	>2.2
Method	Other: DIN 38412 part 11
GLP	no
Source	Huels AG Marl

Toxicity to Aquatic Invertebrates

Species	Scenedesmus subspicatus (Algae)
Endpoint	biomass
Exposure period	72 hour(s)
Unit	mg/l
Analytical monitoring	No
Method	Other: Directive 92/69/EEC, part C
GLP	yes
Remark	EC50 > water solubility (under test conditions)

Source	Huels AG Marl
Test substance	MIGLYOL 812

Toxicity to Microorganisms e.g. Bacteria

Type	aquatic
Species	Pseudomonas putida (Bacteria)
Exposure period	5 hour(s)
Unit	mg/l
Analytical monitoring	No
EC10	>1900
Method	Other: oxygen consumption test (Huels method)
GLP	yes
Remark	Nonylphenol-10EO-5PO was used as solubilizer
Source	Huels AG Marl

As taken from IUCLID Dataset (2000), Glycerides, mixed decanoyl and octanoyl (73398-61-5).

The Ecological Categorization Results from the Canadian Domestic Substances List state that glycerides, mixed decanoyl and octanoyl (CAS RN 73398-61-5) are inherently toxic to aquatic organisms:

Pivotal value for iT (mg/l)	0.685
Comment iT	Group: individual; Subgroup: Other glicerides (individual);
Toxicity to fish (LC50 in mg/l) as predicted by PNN	2.92432
Toxicity to daphnia (EC50 in mg/l) as predicted by Topkat v6.1	0.685
Toxicity to fish, daphnia, algae or mysid shrimp (EC50 or LC50 in mg/l) as predicted by Ecosar v0.99g	0.685
Toxicity to fish (LC50 in mg/l) as predicted by Neutral Organics QSAR in Ecosar v0.99g	6.85E-003

The Ecological Categorization Results from the Canadian Domestic Substances List state that decanoic acid, ester with 1,2,3-propanetriol octanoate (CAS RN 65381-09-1) is inherently toxic to aquatic organisms:

Pivotal value for iT (mg/l)	0.103
Toxicity to fish (LC50 in mg/l) as predicted by PNN	13.6904
Toxicity to daphnia (EC50 in mg/l) as predicted by Topkat v6.1	0.2255
Toxicity to fish, daphnia, algae or mysid shrimp (EC50 or LC50 in mg/l) as predicted by	0.103

Ecosar v0.99g	
Toxicity to fish (LC50 in mg/l) as predicted by Neutral Organics QSAR in Ecosar v0.99g	3.45E-002

Data accessed March 2017 on the OECD website: http://webnet.oecd.org/CCRWeb/Search.aspx

Species: Brachydanio rerio (Fish, fresh water)

Exposure period: 96 hour(s)

Unit: mg/l

LC0: 10000

LC50: > 10000

Method: other: ISO 7346/2 (semistatic)

Related to: Test substance

Source: Henkel KGaA Duesseldorf

Test substance: Active Matter = 100 %

Species: Leuciscus idus (Fish, fresh water)

Exposure period: 48 hour(s)

Unit: mg/l

LC0: > 10000

Method: other: DIN 38412, Teil 15 (Golden orfe, acute toxicity test)

Test substance: as prescribed by 1.1 – 1.4

Remark: Related to: Test substance

Test substance: Active Matter = 100 %

Species: Daphnia magna (Crustacea)

Unit: mg/l

EC0: 1

EC50: 17

EC100: 00

Method: other: DIN 38412, Teil 11 (Daphnia, acute toxicity test)

Method: Method conforms with OECD Guide–line 202, part 1

Remark: Related to: Active Substance Stammsuspension aus 10 g/l, US–Behandlung.

Unit: = 100

EC50: > 100

EC100: > 100

The water–soluble portion of the test substance was not toxic. Only the water phase was tested. Limit test (only one test substance concentration).

Test substance: Active Matter ca. 100 %

Toxicity to Aquatic Plants e.g. Algae

Species: Scenedesmus subspicatus (Algae)

Exposure period: 72 hour(s)

EC0: = 100

Method: other:DIN 38412, Teil 9 (Algal growth inhibition test)

Method: Method conforms with OECD Guide–line 201

EC50: 50

EC10: 7.8

Method: other: DIN 38412, Teil 9 (Algal growth inhibition test)

Remark: Related to: Active Substance Stammsuspension, US–Behandlung

Type: aquatic

Species: Pseudomonas putida (Bacteria)

Exposure period: 30 minute(s)

Unit: mg/l Analytical monitoring: no

EC0: = 10000

Method: other: DIN 38412, Teil 27 (Oxygen consumption test; corresponds to OECD–Guideline 209)

GLP: no

Species: other bacteria: Bifidobacterium bifidum

Method: other: Growth Inhibition–Test

Test substance: other TS: Tricaprin

Result: Neither inhibition nor stimulation of bacterial growth was observed.

EC0: 10000

Method: other: DIN 38412, Teil 27 (Bacterial oxygen consumption test)

Method: Method conforms with OECD Guide–line 209

Related to: Active Substance

Chronic Toxicity to Aquatic Invertebrates

Exposure period: 21 day

NOEC: = 100

LOEC: > 100

Method: other: Daphnia–Life–Cycle–Test (UBA–Proposition February 1984)

Method: Method conforms with OECD Guide–line 202

As taken from IUCLID Dataset (2000), Caprylic/capric triglyceride (65381-09-1).

10.3. Sediment toxicity

No data available to us at this time.

10.4. Terrestrial toxicity

No data available to us at this time.

10.5. All other relevant types of ecotoxicity

EPISuite provides the following data:

Bioaccumulation Estimates (BCFBAF v3.01):

Log BCF from regression-based method:	1.780 (BCF = 60.32 L/kg wet-wt)
Log Biotransformation Half-life (HL):	-1.2168 days (HL = 0.0607 days)
Log BCF Arnot-Gobas method (upper trophic):	1.411 (BCF = 25.77)
Log BAF Arnot-Gobas method (upper trophic):	1.411 (BAF = 25.77)
log Kow used:	5.29 (estimated)

The Ecological Categorization Results from the Canadian Domestic Substances List simply state that glycerides, mixed decanoyl and octanoyl (CAS RN 73398-61-5) and decanoic acid, ester with 1,2,3-propanetriol octanoate (CAS RN 65381-09-1) are not bioaccumulative in the environment.

Data accessed March 2017 on the OECD website: http://webnet.oecd.org/CCRWeb/Search.aspx

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12. Other information

13. Last audited

January 2022

I U C L I D

D a t a s e t

Existing Chemical	Substance ID: 73398–61–5
CAS No.	73398–61–5
EINECS Name	Glycerides, mixed decanoyl and octanoyl
EINECS No.	277–452–2
Molecular Weight	498
Molecular Formula	approximately C29 H54 O6

Dataset created by: EUROPEAN COMMISSION – European Chemicals Bureau

This dossier is a compilation based on data reported by the European Chemicals Industry following 'Council Regulation (EEC) No. 793/93 on the Evaluation and Control of the Risks of Existing Substances'. All (non–confidential) information from the single datasets, submitted in the IUCLID/HEDSET format by individual companies, was integrated to create this document.

The data have not undergone any evaluation by the European Commission.

Creation date: 19–FEB–2000

Number of Pages: **27**

Chapters: **all**

Edition: **Year 2000 CD–ROM edition**

Flags: **non–confidential**

1.0.1 OECD and Company Information

Name: Croda Universal Ltd
Street: Cowick Hall, Snaith
Town: DN14 9AA Goole, North Humberside
Country: United Kingdom
Phone: 0405 860551
Telefax: 0405 860205
Telex: 57601
Cedex: DN14 9AA

Name: Huels AG
Street: Postfach
Town: D–45764 Marl
Country: Germany

1.0.2 Location of Production Site

–

1.0.3 Identity of Recipients

–

1.1 General Substance Information

Substance type: organic
Physical status: liquid

1.1.1 Spectra

–

1.2 Synonyms

C8 und C10–Fettsaeureglycerinester
Source: Huels AG Marl

caprylic/capric triglyceride
Source: Croda Universal Ltd Goole, North Humberside

Decanoyl–octanoyl–triglyceridgemisch
Source: Huels AG Marl

fractionated coconut oil
Source: Croda Universal Ltd Goole, North Humberside

Glyceride, gemischte Decanoyl und Octanoyl
Source: Huels AG Marl

glyceryl tricaprylate/caprate
Source: Croda Universal Ltd Goole, North Humberside

glyceryl trioctanoate/decanoate
Source: Croda Universal Ltd Goole, North Humberside

MCT Oil (Ph. Eur.)
Source: Huels AG Marl

medium chain triglycerides
Source: Croda Universal Ltd Goole, North Humberside

MIGLYOL 812
Source: Huels AG Marl

Mittelkettige Triglyceride
Source: Huels AG Marl

octanoic/decanoic acid triglyceride
Source: Croda Universal Ltd Goole, North Humberside

Softenol 3108
Source: Huels AG Marl

Triglyceride von Capryl- und Caprinsaeure
Source: Huels AG Marl

1.3 Impurities

-

1.4 Additives

-

1.5 Quantity

-

1.6.1 Labelling

-

1.6.2 Classification

-

1.7 Use Pattern

-

1.7.1 Technology Production/Use

-

1.8 Occupational Exposure Limit Values

Type of limit: MAK (DE)
Limit value:
Country: Germany
Remark: value not established
Source: Huels AG Marl

(1)

1.9 Source of Exposure

Memo: Release into the atmosphere at production site
Remark: Release into the atmosphere on production site in 1994: No release
Source: Huels AG Marl

(2)

Remark: Manufactured at one site only by esterification reaction
Source: Croda Universal Ltd Goole, North Humberside

1.10.1 Recommendations/Precautionary Measures

-

1.10.2 Emergency Measures

-

1.11 Packaging

-

1.12 Possib. of Rendering Subst. Harmless

-

1.13 Statements Concerning Waste

-

1.14.1 Water Pollution

Classified by: KBwS (DE)
Labelled by: KBwS (DE)
Class of danger: 0 (generally not water polluting)
Country: Germany
Remark: No. 760 in catalogue
Source: Huels AG Marl

(1)

1.14.2 Major Accident Hazards

Legislation: Stoerfallverordnung (DE)
Substance listed: no
Country: Germany
Remark: Stoerfallverordnung 1991
Source: Huels AG Marl

(1)

1.14.3 Air Pollution

Classified by: other: Huels AG
Labelled by: other: Huels AG
Number: 3.1.7 (organic substances)
Class of danger: III
Country: Germany
Source: Huels AG Marl

1.15 Additional Remarks

-

1.16 Last Literature Search

-

1.17 Reviews

-

1.18 Listings e.g. Chemical Inventories

-

2.1 Melting Point

Value: ca. 0 – 10 degree C
Decomposition: no
Sublimation: no
GLP: no
Source: Huels AG Marl

(3)

Value: < 0 degree C
Decomposition: no
Sublimation: no
GLP: no
Remark: cloud point
Source: Huels AG Marl

(4)

2.2 Boiling Point

–

2.3 Density

Type: density
Value: ca. .95 g/cm3 at 20 degree C
GLP: no
Source: Huels AG Marl

(5) (4)

2.3.1 Granulometry

–

2.4 Vapour Pressure

Value: < .01 hPa at 20 degree C
GLP: no
Source: Huels AG Marl

(4)

2.5 Partition Coefficient

log Pow: > 3 at 23 degree C
Method: OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year: 1981
GLP: no
Source: Huels AG Marl

(6)

2.6.1 Water Solubility

Value: < 10 mg/l at 20 degree C
Qualitative: of very low solubility
Source: Huels AG Marl

(4)

2.6.2 Surface Tension

-

2.7 Flash Point

Value: ca. 220 degree C
Type: open cup
Method: other: DIN ISO 2592
Year:
GLP: no
Source: Huels AG Marl

(5) (4)

2.8 Auto Flammability

-

2.9 Flammability

-

2.10 Explosive Properties

-

2.11 Oxidizing Properties

-

2.12 Additional Remarks

-

3.1.1 Photodegradation

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 500000 molecule/cm3
Rate constant: = .0000000000294998 cm3/(molecule * sec)
Degradation: = 50 % after .5 day
Method: other (calculated): AOP Computer Program, Vers. 1.53, Syracuse Research Center (basedon Reference)
Year: 1994 **GLP:**
Test substance:
Remark: The OH concentration represents 24 hour average, thus the half–life refers to 24 hour–days.
A triester with two n–octyl and one n–decyl alcohol components was chosen for the calculation.
Source: Huels AG Marl

(7)

3.1.2 Stability in Water

–

3.1.3 Stability in Soil

–

3.2 Monitoring Data (Environment)

–

3.3.1 Transport between Environmental Compartments

–

3.3.2 Distribution

–

3.4 Mode of Degradation in Actual Use

–

3.5 Biodegradation

Type: aerobic
Inoculum: activated sludge, domestic, non–adapted
Concentration: 36.5 mg/l related to Test substance
Degradation: = 93 % after 28 day
Result: readily biodegradable
Method: other: ISO 10708 (draft): BODIS (Blok) Test
Year: 1993 **GLP:** yes
Test substance: as prescribed by 1.1 – 1.4
Source: Huels AG Marl

(8)

3.6 BOD5, COD or BOD5/COD Ratio

–

3.7 Bioaccumulation

–

3.8 Additional Remarks

–

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: semistatic
Species: Brachydanio rerio (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** yes
LC0: >= 53
Method: other: Directive 92/69/EEC, C.1
Year: 1992 **GLP:** yes
Test substance: as prescribed by 1.1 – 1.4
Remark: No toxic effects were observed below the water solubility (under test conditions).
Source: Huels AG Marl
Test substance: MIGLYOL 812

(9)

Type: static
Species: Leuciscus idus (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no
LC0: >= 1000
Method: other: Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische, DIN38412 Teil 15
Year: **GLP:** no
Test substance: as prescribed by 1.1 – 1.4
Remark: An emulsifier (MARLOWET EF) was added.
Source: Huels AG Marl

(10)

4.2 Acute Toxicity to Aquatic Invertebrates

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC0: >= 2.2
EC50: > 2.2
Method: other: DIN 38412 part 11
Year: **GLP:** no
Test substance: as prescribed by 1.1 – 1.4
Source: Huels AG Marl

(11)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Scenedesmus subspicatus (Algae)
Endpoint: biomass
Exposure period: 72 hour(s)
Unit: mg/l **Analytical monitoring:** no
Method: other: Directive 92/69/EEC, part C
Year: 1992 **GLP:** yes
Test substance: as prescribed by 1.1 – 1.4
Remark: EC50 > water solubility (under test conditions)
Source: Huels AG Marl
Test substance: MIGLYOL 812

(12)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: Pseudomonas putida (Bacteria)
Exposure period: 5 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC10: > 1900
Method: other: Oxygen consumption test (Huels method)
Year: **GLP:** yes
Test substance: as prescribed by 1.1 – 1.4
Remark: Nonylphenol–10EO–5PO was used as solubilizer
Source: Huels AG Marl

(13)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

–

4.5.2 Chronic Toxicity to Aquatic Invertebrates

–

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Soil Dwelling Organisms

–

4.6.2 Toxicity to Terrestrial Plants

–

4.6.3 Toxicity to other Non–Mamm. Terrestrial Species

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4.7 Biological Effects Monitoring

–

4.8 Biotransformation and Kinetics

–

4.9 Additional Remarks

–

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: > 34000 mg/kg bw
Method:
Year: **GLP:** no
Test substance: as prescribed by 1.1 – 1.4
Remark: Groups of 10 rats (Wistar, male) received 4.5, 9.0, 18.0 or 36.0 ml/kg of undiluted test substance per gavage; no animal died during the study; 10 days after dosing all animals were sacrificed and submitted to autopsy; no pathological changes were observed.
Source: Huels AG Marl

(14)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: > 5000 mg/kg bw
Method:
Year: **GLP:** no data
Test substance: no data
Remark: Test material produced no mortality in male or female rats; all animals showed no changes in appearance or behavior and presented no abnormalities at necropsy 14 days after treatment; no further details reported.
Source: Huels AG Marl

(15)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: > 5000 mg/kg bw
Method:
Year: **GLP:** no data
Test substance: no data
Remark: Test material produced no mortality in male or female rats; all animals showed no changes in appearance or behavior and presented no abnormalities at necropsy 14 days after treatment; no further details reported.
Source: Huels AG Marl

(16)

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Value: > 23750 mg/kg bw
Method:
Year: **GLP:** no
Test substance: as prescribed by 1.1 – 1.4
Remark: Groups of 10 female mice of Tyler’’s Original Strain each were dosed with undiluted test material per gavage (12.5, 20.0 or 25.0 ml/kg); lethargy, ataxia and dyspnea occurred within 15 minutes after dosing in the highest dosage group; 1 animal of the highest dosage group and 2 animals of the mid dosage group died 24–48 hours after dosing; all symptoms disappeared in the survivors by the end of the third day.
Source: Huels AG Marl

(17)

5.1.2 Acute Inhalation Toxicity

–

5.1.3 Acute Dermal Toxicity

–

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.p.
Value: > 22800 mg/kg bw
Method:
Year: **GLP:** no
Test substance: as prescribed by 1.1 – 1.4
Remark: Animals were injected intraperitoneally with single doses of the test substance ranging from 1 to 24 ml/kg (1.0, 2.0, 4.0, 8.0, 16.0 or 24.0 ml/kg; 5 male rats/dose); all animals were sacrificed 14 days after dosing and submitted to autopsy; no death occurred during the study; no signs of toxicity or treatment related effects were observed.
Source: Huels AG Marl

(14)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: not irritating
EC classificat.:
Method: other: EPA guidelines, (FIFRA, TSCA)
Year: **GLP:**
Test substance: as prescribed by 1.1 – 1.4
Remark: irritation index: 0/8
Source: Huels AG Marl

(18)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: not irritating
EC classificat.:
Method:
Year: **GLP:** no
Test substance: as prescribed by 1.1 – 1.4
Remark: 3 male animals; the test substance was applied for 24, 48, and 72 hours; no irritating effects were observed.
Source: Huels AG Marl

(14)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: not irritating
EC classificat.:
Method: other: Performed by an official French method (Journal Official de laRepublique Francaise)
Year: **GLP:**
Test substance: as prescribed by 1.1 – 1.4
Remark: irritation index: 0,21/8
Source: Huels AG Marl

(19)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: not irritating
EC classificat.:
Method:
Year: **GLP:** no data
Test substance: no data
Remark: irritation index: 0/8
3 rabbits/sex, 0.5 ml of undiluted test material was applied to abraded and non–abraded skin, occluded patch; observation period: 24 and 72 hours after treatment; no further details reported.
Source: Huels AG Marl

(16)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: not irritating
EC classificat.:
Method:
Year: **GLP:** no data
Test substance: no data
Remark: irritation index: 0.25/8
6 rabbits (sex unspec.), 0.5 ml of undiluted test material was applied to abraded and non–abraded skin, occluded patch; observations were made 24 and 72 hours after treatment; no further details reported.
Source: Huels AG Marl

(16)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: not irritating
EC classificat.:
Method:
Year: **GLP:** no data
Test substance: no data
Remark: irritation index: 0.05/8
3 rabbits/sex, no further details reported.

Source: Huels AG Marl
(15)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: not irritating
EC classificat.:
Method:
Year: **GLP:** no
Test substance: no data
Remark: irritation index: 0.92/8
6 rabbits (sex unspec.), no further details reported.
Source: Huels AG Marl
(20)

5.2.2 Eye Irritation

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: not irritating
EC classificat.:
Method: other: EPA guidelines, (FIFRA, TSCA)
Year: **GLP:**
Test substance: as prescribed by 1.1 – 1.4
Remark: irritation index: 2,04/110 (according to Draize)
cornea : x = 0
iris : x = 0
––––––––––––––
conjunctiva:
–redness : x = 0,16
–chemosis: x = 0,16
the treated eye of one rabbit showed transient inflammation one hour after treatment; all treated eyes appeared normal 24 to 48 hours after treatment.
Source: Huels AG Marl
(21)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: not irritating
EC classificat.:
Method: Draize Test
Year: **GLP:** no
Test substance: as prescribed by 1.1 – 1.4
Remark: No corneal nor iris damage was seen during the study; conjunctival irritation was very slight.
Source: Huels AG Marl

(22)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: not irritating
EC classificat.:
Method:
Year: **GLP:** no
Test substance: as prescribed by 1.1 – 1.4
Remark: 0.5 ml of the test substance were applied once daily to 3 male rabbits on 6 consecutive days; no irritating effects were observed.
Source: Huels AG Marl

(14)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: not irritating
EC classificat.:
Method: other: Performed by an official French method (Journal Official de laRepublique Francaise)
Year: **GLP:**
Test substance: as prescribed by 1.1 – 1.4
Remark: irritation index: 2/110
Source: Huels AG Marl

(19)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: not irritating
EC classificat.:
Method: Draize Test
Year: **GLP:** no data
Test substance: no data
Remark: irritation index: 0/110
6 rabbits, observations were made after 24, 48 and 72 hours, no further details reported.
Source: Huels AG Marl

(16)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: not irritating
EC classificat.:
Method: Draize Test
Year: **GLP:** no data
Test substance: no data
Remark: irritation index: 0/110
6 rabbits, observation were made 24, 48, 96 and 108 hours after treatment; no further details reported.
Source: Huels AG Marl

(16)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: not irritating
EC classificat.:
Method: Draize Test
Year: **GLP:** no data
Test substance: no data
Remark: 6 rabbits, observations were made 24, 48, 72 and 96 hours after treatment; a very mild, transient conjunctival redness and discharge was reported, resulting in scores of 0.7/110 (24 hours) and 0.3/110 (48 and 96 hours); no further details reported.
Source: Huels AG Marl

(15)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: not irritating
EC classificat.:
Method: Draize Test
Year: **GLP:** no
Test substance: no data
Remark: irritation index: 0/110
6 rabbits, observations were made 24, 48 and 72 hours after treatment; no further details reported.
Source: Huels AG Marl

(20)

5.3 Sensitization

Type: other: skin sensitisation
Species: guinea pig
Number of Animals:
Vehicle:
Result: not sensitizing
Classification:
Method:
Year: **GLP:** no
Test substance: as prescribed by 1.1 – 1.4
Remark: The test substance was applied as a 4% solution in ethanol to closely clipped areas on the backs and flanks every other day for 10 days; 24 hours after each application erythema and edema readings were zero in all cases; the challenge application was made 2 weeks after the last priming dose; 0/6 animals showed sensitization 24 hours after the challenge application.
Source: Huels AG Marl

(23)

5.4 Repeated Dose Toxicity

Species: rat **Sex:** male
Strain: Wistar
Route of admin.: oral feed
Exposure period: 3 months
Frequency of treatment: daily
Post. obs. period: –
Doses: 10000 ppm, 50000 ppm
Control Group: yes
Method:
Year: **GLP:** no
Test substance: as prescribed by 1.1 – 1.4
Remark: 20 male rats/dose; 20 male and 20 female rats/control; urine analysis and blood counts were done in the middle and at the end of the feeding period; serum GOT and GPT transaminases and free and esterified fatty acids were measured when the animals were sacrificed; no death occured during the study; no treatment related effects on behavior, food intake, weight gain, relative organ weights or on histological findings were observed.
Source: Huels AG Marl

(14)

Species: rat **Sex:** male/female
Strain: Wistar
Route of admin.: oral feed
Exposure period: 47 weeks
Frequency of treatment: daily
Post. obs. period: none
Doses: –
Control Group: no
Method:
Year: **GLP:** no
Test substance: no data
Remark: Rats were fed a diet containing 19,6 % of a triglyceride composed of 75 % caprylic acid and 25 % of capric acid (MCT); controls were fed a diet which differed only in the source of dietary fat (oleo oil, butter fat, coconut oil, corn oil); safflower oil was added to all diets containing MCT to insure adequacy of the essential fatty acids; the MCT containing diet supported normal growth and development, though growth rate was slightly less than that of rats fed the other diets; mortality was not markedly different between the groups; at autopsy, the carcass protein, ash levels and organ weights of test rats were similar to those of control rats, but there was less carcass fat and smaller epididymal fat pads in the test group; histological study revealed no abnormalities in intestine and liver.
Source: Huels AG Marl

(24)

Species: rat **Sex:** male
Strain: Wistar
Route of admin.: gavage
Exposure period: 30 days
Frequency of treatment: daily (7 days/week)
Post. obs. period: –
Doses: 1,0 or 3,0 ml/rat
Control Group: yes
Method:
Year: **GLP:** no
Test substance: as prescribed by 1.1 – 1.4
Remark: 10 rats/dose or control group;
the average doses were 7200 or 20200 mg/kg; weight gains of the treatment groups and the control group did not differ significantly; no signs of toxicity and no treatment related death was observed; animals of the lower dosage group showed no abnormal appearance or behavior and no urinary changes throughout the test; animals of the higher dosage group exhibited a decrease in appetite, fatty feces and a shaggy coat in the first five to seven days; all animals were submitted to autopsy at the end of the study and showed no pathological changes.
Source: Huels AG Marl

(14)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: Salmonella typhimurium TA 97, TA 98, TA 100
Concentration: 0 – 1000 ug/plate
0 – 1000 ug/plate
0 – 1000 ug/plate
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 – 1.4
Remark: Only one test with three strains was performed;
solvent: DMSO
test was performed in presence and absence of liver S–9 of aroclor treated rats; the test substance did not induce mutations in this test system.
Source: Huels AG Marl

(25)

5.6 Genetic Toxicity 'in Vivo'

–

5.7 Carcinogenicity

–

5.8 Toxicity to Reproduction

-

5.9 Developmental Toxicity/Teratogenicity

-

5.10 Other Relevant Information

Type: Biochemical or cellular interactions
Remark: 5 rabbits received a single injection of 0.5 ml of test material in both thigh muscles; another group of 5 animals received 0.2 ml of test material 3 times/week for 2 weeks by the same way; all animals were sacrificed 48 hours after the last application; no signs of topical reactions were observed.
Source: Huels AG Marl

(26)

Type: Biochemical or cellular interactions
Remark: 3 rabbits received a single injection of 0.5 ml of test material in both thigh muscles; another group of 3 animals received the test substance (0.5 ml) 3 times/week for 2 weeks by the same way; all animals were sacrificed 48 hours after the last application; no signs of topical reactions and no pathological abnormalities at the injection site were observed.
Source: Huels AG Marl

(27)

Type: Biochemical or cellular interactions
Remark: 4 rabbits received a single injection of 0.5 ml test material in both thigh muscles; 2 animales were sacrificed 5 days after application, the remaining animals 14 days after application; 4 other animals were treated in the same way with olive oil; no treatment related adverse effects were observed; microscopic examination revealed no pathological changes.
Source: Huels AG Marl

(28)

Type: Biochemical or cellular interactions
Remark: 5 rabbits received 0.5 ml of test material 2 times/week for 90 days by injection in both thigh muscles; the animals were sacrificed 48 hours after the last application; blood samples taken before treatment started and before its termination showed no effects on total lipids or cholesterol levels, nor on hemoglobin, red and white cell counts and the differential blood picture; there were no indications of pathological effects in the large parenchymatous organs and no fatty degeneration of pulmonary fatty embolism.
Source: Huels AG Marl

(28)

Type: other: acute i.v. toxicity
Remark: The acute toxicity by intravenous injection of emulsions of triglycerides of fatty acids (C2–C11) to mice was determined. Triglycerides were injected as 10 % or 25 % emulsions in glucose solution, containing phosphatides and polyglycerol mono–oleate; each type of emulsion was administered to at least 6 groups of 10 mice each.
LD50 of C8–triglycerid : 3700 +–194 mg/kg
LD50 of C10–triglycerid : >10000 mg/kg
Source: Huels AG Marl

(29)

Type: other: acute inhalation toxicity
Remark: 10 male rats (Sprague–Dawley) and 10 guinea pigs (Birbright White/W 58) were exposed for six hours to an aerosol of the test substance at a concentration of 28,1 ug/l of air; the fraction with particles small enough to be inhaled into the lung (<5 um) represented 1,97 ug/l of air; three animals of each species were exposed to air and served as control.
One hour after the exposure three animals and one control of each species were sacrificed for pathological examination, the remaining animals were sacrificed 14 days after exposure; no death occurred throughout the study; observation during the exposure and for 14 days thereafter revealed no symptoms, abnormal behavior or effects on body weight; no treatment related gross or microscopic defects were detected.
Source: Huels AG Marl

(30)

Type: other: repeated dose toxicity study with chicken
Remark: A three week feeding study (16 % of test material in the diet) was conducted with 12 male chicken (White Leghorn), 12 male chicken served as control;
the control and test diet were not palatable to the animals, resulting in reduced feed consumption (control group – 954 g, test group – 786 g) and reduced body weight gain for both groups; all mortalities (3 animals of the control group, 4 animals of the test group) seemed to reflect diet rejection and did not appear related to the test material; gross autopsy did not reveal any abnormal liver or kidney changes.
Source: Huels AG Marl

(31)

Type: other: reproductive toxicity
Remark: In a reproduction study young adult male and female rats (Mc Collum–Wisconsin Strain) were fed a diet containing 19.6 % of a triglyceride of 75 % caprylic and 25 % capric acid for three weeks before mating; litter size and birth weight of the test animals were similar to those of rats on conventional or low fat diets, but mortality during lactation was somewhat higher and there was less weight gain due to a smaller volume of milk secreted; after weaning the F1 generation was fed as the F0 generation had been and showed a weight gain comparable to that of control rats on an oleo oil diet.
Source: Huels AG Marl

(24)

Type:
Remark: The test material (10, 20 and 50% solutions of caprylic/capric triglycerides in paraffin liquid DAB6) was dropped into one eye each of two test persons at four– to six–day intervals; an additional five male subjects were tested with the undiluted substance; no incompatibility reactions occurred; no further details reported.
Source: Huels AG Marl

(32)

5.11 Experience with Human Exposure

Remark: The test substance was applied to human skin (n=20) for 30 min; after removal of the test substance the skin was exposed to UV light for up to 11,2 min; 8–methoxy–psoralene served as a positive control substance; no erythema was observed 24 or 48 hours after exposure; whereas at the areas of psoralene treatment, erythema were observed.
Source: Huels AG Marl

(33)

Remark: 100 patients were tested with patches of tissue paper saturated with the test material (caprylic/capric triglycerides) for 48 hours; no positive reactions occurred; no further details reported.
Source: Huels AG Marl

(34)

Remark: 128 adult males and females were tested with the test material using a modification of the Draize repeated insult patch test; all subjects had little or no irritation and none was sensi– tized; one subject had barely perceptible erythema at the first reading immediately following the removal of the first patch which had been applied for 48 hours; no further details reported
Source: Huels AG Marl

(35)

Remark: 12 women were tested with 0.4 ml of the test material on each patch; patches were applied daily to the same site for 21 consecutive days; they were removed 23 hours after application and read at 24 hours; one subject had a score of 1/3 on day 16; all other scores were reported to be 0; no further details reported.
Source: Huels AG Marl

(35)

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(4) Huels AG: Sicherheitsdatenblatt "MIGLYOL 812", Version 05, 13.01.95

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(33) Dynamit Nobel AG (1980): Ippen, H., university of Goettingen, unpublished data.

(34) Degos, R., Hospital St. Louis, Paris (1968)
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J. Environ. Pathol. Toxicol. 4, 105–120 (1980).

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7.1 Risk Assessment

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European Food Safety Authority

EFSA Journal 2011;9(6):2240

SCIENTIFIC OPINION

Scientific Opinion on the substantiation of health claims related to medium-chain triglycerides and reduction in body weight (ID 643, 677, 1614) pursuant to Article 13(1) of Regulation (EC) No 1924/2006[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

SUMMARY

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies was asked to provide a scientific opinion on a list of health claims pursuant to Article 13 of Regulation (EC) No 1924/2006. This opinion addresses the scientific substantiation of health claims in relation to medium-chain triglycerides and reduction in body weight. The scientific substantiation is based on the information provided by the Member States in the consolidated list of Article 13 health claims and references that EFSA has received from Member States or directly from stakeholders.

The food constituent that is the subject of the health claims is medium-chain triglycerides. In the context of the references provided, the Panel assumes that the food constituent which is the subject of the health claims is medium-chain fatty acids, which should replace long-chain fatty acids in triglycerides in order to obtain the claimed effect. The Panel considers that the food constituent, medium-chain fatty acids, which is the subject of the health claims, is sufficiently characterised in relation to the claimed effect.

The claimed effect is "weight management". The target population is assumed to be overweight individuals in the general population who wish to reduce their body weight. The Panel considers that reduction in body weight is a beneficial physiological effect.

In weighing the evidence, the Panel took into account that the results from the human intervention studies provided are inconsistent with respect to the effects of medium-chain triglycerides on body weight loss, and that the evidence in support of a mechanism by which medium-chain triglycerides could exert the claimed effect is weak and not convincing.

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[1] On request from the European Commission, Question No EFSA-Q-2008-1430, EFSA-Q-2008-1464, EFSA-Q-2008-2350, adopted on 08 April 2011.

[2] Panel members: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Hannu Korhonen, Pagona Lagiou, Martinus Løvik, Rosangela Marchelli, Ambroise Martin, Bevan Moseley, Monika Neuhäuser-Berthold, Hildegard Przyrembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Stephan Strobel, Inge Tetens, Daniel Tomé, Hendrik van Loveren and Hans Verhagen. Correspondence: nda@efsa.europa.eu

[3] Acknowledgement: The Panel wishes to thank for the preparatory work on this scientific opinion: The members of the Working Group on Claims: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Marina Heinonen, Hannu Korhonen, Martinus Løvik, Ambroise Martin, Hildegard Przyrembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Inge Tetens, Hendrik van Loveren and Hans Verhagen. The members of the Claims Sub-Working Group on Weight Management/Satiety/Glucose and Insulin Control/Physical Performance: Kees de Graaf, Joanne Harrold, Mette Hansen, Mette Kristensen, Anders Sjödin and Inge Tetens.

Suggested citation: EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on the substantiation of health claims related to medium-chain triglycerides and reduction in body weight (ID 643, 677, 1614) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 2011;9(6):2240. [17 pp.]. doi:10.2903/j.efsa.2011.2240. Available online: www.efsa.europa.eu/efsajournal

The Panel concludes that a cause and effect relationship has not been established between the consumption of medium-chain triglycerides and reduction in body weight.

KEY WORDS

Medium-chain triglycerides, long-chain triglycerides, replacement, body weight, health claims.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

See Appendix A

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

See Appendix A

EFSA DISCLAIMER

See Appendix B

INFORMATION AS PROVIDED IN THE CONSOLIDATED LIST

The consolidated list of health claims pursuant to Article 13 of Regulation (EC) No 1924/2006[4] submitted by Member States contains main entry claims with corresponding conditions of use and literature for similar health claims. EFSA has screened all health claims contained in the original consolidated list of Article 13 health claims which was received by EFSA in 2008 using six criteria established by the NDA Panel to identify claims for which EFSA considered sufficient information had been provided for evaluation and those for which more information or clarification was needed before evaluation could be carried out[5]. The clarifications which were received by EFSA through the screening process have been included in the consolidated list. This additional information will serve as clarification to the originally provided information. The information provided in the consolidated list for the health claims which are the subject of this opinion is tabulated in Appendix C.

ASSESSMENT

1. Characterisation of the food/constituent

The food constituent that is the subject of the health claims is medium-chain triglycerides (MCTs).

In the context of the references provided, the Panel assumes that the food constituent which is the subject of the health claims is medium-chain fatty acids (MCFAs), which should replace long-chain fatty acids (LCFAs) in triglycerides in order to obtain the claimed effect. In the context of the references provided, the Panel assumes that MCFAs (6-10 carbon atoms), mostly caprylic (C:8) and capric (C:10) acids in a ratio of approximately 2-3 to 1 in the form of triglycerides, should replace LCFAs (>12 carbon atoms) in the form of triglycerides (LCTs) in order to obtain the claimed effect.

The Panel considers that the food constituent, MCTs, which is the subject of the health claims, is sufficiently characterised in relation to the claimed effect.

2. Relevance of the claimed effect to human health (ID 643, 677, 1614)

The claimed effect is "weight management". The Panel assumes that the target population is overweight individuals in the general population who wish to reduce their body weight.

In the context of the proposed wordings and the references provided, the Panel assumes that the claimed effect refers to reduction in body weight.

Weight loss can be interpreted as the achievement of a normal body weight in previously overweight subjects. In this context, weight loss in overweight subjects without achieving a normal body weight is considered to be a beneficial physiological effect.

The Panel considers that reduction in body weight is a beneficial physiological effect.

3. Scientific substantiation of the claimed effect (ID 643, 677, 1614)

The majority of the references provided for the scientific substantiation of the claim reported on the effects of food constituents other than MCTs and/or on health outcomes (e.g. acute or short-term

[4] Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

[5] EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2011. General guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims. EFSA Journal, 9(4):2135, 24 pp.

effects on appetite ratings, energy intake, fat oxidation and/or regulatory hormone concentrations, blood lipids, energy expenditure, and body composition) other than body weight. The Panel considers that no conclusions can be drawn from these references for the scientific substantiation of the claim.

A total of ten publications reporting on nine human intervention studies which addressed the effects of MCT *vs.* LCT consumption on body weight were provided (Beermann et al., 2003; Han et al., 2007; Kasai et al., 2003; Krotkiewski, 2001; Nosaka et al., 2003; St-Onge and Jones, 2003; St-Onge et al., 2003a; St-Onge et al., 2003b; Tsuji et al., 2001; Yost and Eckel, 1989). Two publications reported on the same study (St-Onge and Jones, 2003; St-Onge et al., 2003b).

Two of the studies were designed to assess the metabolic effects of replacing LCTs by MCTs, and had a randomised, parallel design, a duration of two and four weeks, and included five and eight subjects per intervention group, respectively (Beermann et al., 2003; Yost and Eckel, 1989). The Panel notes the small sample size of these studies, which may have been inappropriate to assess changes in body weight, and considers that no conclusions can be drawn for the scientific substantiation of the claim.

In a parallel, randomised, double-blind intervention study (Tsuji et al., 2001), the effects on body weight of 10 g/day MCTs were compared to the effects of 10g/day LCTs (blended rapeseed oil and soybean oil) in bread consumed daily at breakfast for 12 weeks in healthy men and women. A total of 100 subjects were randomised but only 78 completed the study and entered data analysis. Dietary counselling was provided to all subjects at the beginning of the study. Compliance with the study diet aiming to maintain energy balance was self-reported. Body weight was measured at weeks 0, 4, 8 and 12. Data from subjects with BMI ≥23 kg/m^2 or <23 kg/m^2 were presented separately. Data analyses for the entire study population were not provided. It is unclear whether this sub-group analysis was planned at recruitment [(BMI ≥23 kg/m^2: n=26 (MCTs), n=30 (LCTs); BMI <23 kg/m^2: n=15 (MCTs), n=7 (LCTs)]. The differences in raw data were examined by two-way ANOVA. The significance of differences between the groups for the same period was assessed by unpaired Student's *t*-test (two-tailed). It is unclear from the publication whether initial body weight was included as a covariate in the two-way ANOVA, or whether the MCT and LCT groups were comparable at baseline regarding body weight (mean±SEM=75.7±1.9 kg *vs.* 72.8 ±1.1 kg). The Panel notes the substantial limitations of the study, and considers that no conclusions can be drawn from it for the scientific substantiation of the claim.

In a randomised, cross-over, controlled feeding intervention (St-Onge et al., 2003a), the effects on body weight of diets rich in either MCTs or LCTs (as olive oil) for periods of four weeks each were assessed in 17 healthy obese women. Diets contained 40 % of energy as fat, 15 % as protein and 45 % as carbohydrates, were designed for body weight maintenance, and all meals were provided to the subjects for the duration of the study under strictly controlled conditions. Of the total amount of fat, 75 % was derived from either beef tallow (LCTs) or a blend of saturated and unsaturated vegetable oils (MCTs). In the MCT diet, 50 % of the total fat was provided by MCT oil, rich in octanoate and decanoate (49 and 50 % of total fatty acids respectively), 10 % by olive oil and 5 % each by butter, coconut oil and flaxseed oil. An unesterified plant sterol/stanol mixture at a level of 22 mg/kg body weight/day was added to the MCT diet to maintain normal cholesterol concentrations. Wash-out periods were of 4-8 weeks to ensure that all women were assessed in the same phase of the menstrual cycle. No significant differences in weight loss between the two study phases were observed (-0.87±0.16 kg *vs.* -0.84±0.22 kg during MCT and LCT consumption, respectively). The Panel notes that this study did not show a significant effect of MCTs on body weight at doses of about 55 g/day for four weeks in the context of a diet aiming at energy balance.

In a randomised, cross-over, controlled feeding trial (St-Onge and Jones, 2003; St-Onge et al., 2003b), the effects on body weight of diets rich in either MCTs or LCTs (as olive oil) for periods of four weeks each were assessed in 24 healthy overweight men. Diets contained 40 % of energy as fat, 15 %

as protein and 45 % as carbohydrate, and were designed for body weight maintenance. The diets were identical except for the quality of the fat. The MCT-containing diet contained an oil composed of 64.7 % MCT oil, 12.6 % olive oil, 6.8 % each of canola and flaxseed oil, and 5.8 % coconut oil as the main source of fat (75 % of total fat). The control diet (LCTs) contained 75 % of total fat as olive oil. The MCT oil also contained 3.4 % unesterified stanol/sterol mixture. No significant differences in weight loss between the two study phases were observed (-1.03±0.25 kg *vs.*-0.62±0.29 kg during MCT and LCT consumption, respectively). The Panel notes that this study did not show a significant effect of MCTs on body weight at doses of >55 g/day for four weeks in the context of a diet aiming at energy balance.

In a parallel, randomised, double-blind intervention trial (Krotkiewski, 2001), the effects on body weight of MCT *vs*. LCT supplementation during a very low calorie diet (VLCD) were assessed. Three groups of matched obese women (BMI >30 kg/m^2) received an isoenergetic (578.5 kcal) VLCD enriched with MCTs (8.0 g/100g providing 8 kcal/g, n=22) or LCTs (9.9 g/100 g providing 9 kcal/g, n=22), or a low-fat (3.0 g/100 g, n=22) and high-carbohydrate regimen. The diets were administered over four weeks. Body weight significantly decreased in the MCT group compared to the LCT and low-fat group at weeks 1 and 2 of the study, but no significant differences in body weight changes were observed between groups at the end of the study (weeks 3 and 4). The Panel notes that this short-term study did not show a significant effect of MCTs on body weight.

In a parallel, randomised, double-blind intervention trial (Han et al., 2007), the effects on body weight of a test oil with MCTs (extracted from coconut oil, 100 % MCTs with a caprylic acid:capric acid ratio of 2:1) as compared to corn oil (control LCTs), at doses of 18 g/day administered as part of the daily diet were assessed in 40 free-living subjects with type-2 diabetes mellitus living in an urban area of China. Subjects were on treatment with oral antidiabetic medication (sulfonylureas, biguanides or α-glucosidase inhibitors), which were maintained constant during the study. All subjects completed the study and reported being fully compliant with the intervention. Body weight was assessed on days 0, 45 and 90 of the study. Differences between groups at the same time point were assessed using ANOVA, with baseline data as covariate, and Tukey *post-hoc* tests. Body weight in the MCT group was significantly lower than in the LCT group at days 45 and 90 of the study ($p<0.05$; $p=0.012$ for the time-group interaction). Body weight decreased in the MCT group by approximately 1.5 kg, and increased by approximately 0.28 kg in the LCT group. The authors reported that no significant effect of medication use on body weight was detected in either group. However, the Panel notes that this effect was not formally tested in the study, and that the information provided is limited to the type of medication received by each study subject. A significant reduction in energy and fat intake assessed using a three-day weighed food record (first and last week of the study) was also observed in the MCT group compared to the LCT group. The Panel notes that a body weight difference of about -1.7 kg in 12 weeks in favour of MCTs was observed in this study at doses of 18 g/day without imposed energy restriction.

In a parallel, randomised, double-blind intervention trial (Nosaka et al., 2003), the effects on body weight of margarines (14 g/day) containing 5 g of MCTs or an equal amount of LCTs (blended rapeseed oil and soybean oil) consumed with bread at breakfast for 12 weeks were studied. Of the 73 subjects (18 female) recruited and randomised, two dropped out for reasons unrelated to the study, and seven subjects were excluded from data analysis owing to protocol violation. Data analyses were conducted in the population of completers (n=64, n=33 in the MCT group) only. Dietary counselling was provided to all subjects at the beginning of the study. Compliance with the study diet aiming to maintain energy balance was self-reported. Body weight was measured at weeks 0, 4, 8 and 12. A significant reduction in body weight ($p<0.05$) was observed at week 12 in the MCT group as compared to the LCT group (mean±SD=-4.2±2.8 kg *vs.*-2.9±2.0 kg) The Panel notes that a weight difference of about -1.3 kg in 12 weeks in favour of MCTs was observed at doses of 5 g/day in the context of an isoenergetic diet, and that differences in body weight between the MCT and LCT groups were only significant at week 12 of the study.

In a parallel, randomised, double-blind intervention trial (Kasai et al., 2003), the effects on body weight of a test bread made with 14 g of cooking oil (obtained by transesterification of 14 % MCTs and 85 % rapeseed oil) with structured medium and long-chain triglycerides (MLCTs) containing 1.7 g MCFAs were compared to the effects of a bread made with LCTs (blended rapeseed oil and soybean oil). Bread or control breads were consumed daily at breakfast for 12 weeks. Of the 93 subjects recruited and randomised, 10 could not consume the specified meal, and one subject dropped out. Data analyses were conducted in the population of completers (n=82, 7 female, n=40 in the MCT group, 4 female) only. Dietary counselling was provided to all subjects at the beginning of the study. Compliance with the study diet aiming to maintain energy balance was self-reported. Body weight was measured at weeks 0, 4, 8 and 12. A significant reduction in body weight ($p<0.05$) was observed at weeks 4, 8 and 12 in the MCT group as compared to the LCT group (mean±SEM=-2.4±0.2 kg, -3.5±0.3 kg, -4.5±0.4 kg in the MCT group at weeks 4, 8 and 12 as compared to -1.7±0.2 kg; -2.5±0.3 kg; -3.3±0.4 kg in the LCT group). The Panel notes that a weight difference of about -1.2 kg in 12 weeks in favour of MCTs was observed at doses of 1.7 g/day in the context of an isoenergetic diet, and that differences in body weight between the MCT and LCT groups were already significant at 4 weeks (body weight loss difference of about -0.7 kg in favour of MCTs).

The Panel notes that three human intervention studies of 12 week duration observed a significant effect of MCTs on body weight loss at MCT doses of 1.7-18 g/day in the context of diets aiming at energy balance (Han et al., 2007; Kasai et al., 2003; Nosaka et al., 2003), and that the body weight difference between the MCT and LCT groups (range 1.3-1.7 kg) was rather uniform and apparently independent of the MCT doses used. The Panel also notes that one of the studies already observed a significant effect of MCTs on body weight at four weeks (Kasai et al., 2003) using 1.7 g/day MCTs, whereas no effect of MCTs was reported at the same time point at higher doses (>50 g/day) in the context of isoenergetic (St-Onge and Jones, 2003; St-Onge et al., 2003a; St-Onge et al., 2003b) or energy-restricted (Krotkiewski, 2001) diets in more strictly controlled studies.

A number of possible mechanisms by which MCTs could exert the claimed effect have been proposed, and the evidence for these has been reviewed by Kovacs and Mela (2006). MCTs are readily hydrolysed by lipases in the gastro-intestinal tract, and unlike LCTs are directly absorbed into the portal circulation and transported to the liver for oxidation. The intra-mitrochondrial transport of MCTs does not require carnitine palmitoyltransferase, which possibly accelerates oxidation of MCTs and possibly limits storage within tissues. However, the exact mechanism by which MCTs could have an effect on energy balance is unclear. In animals, there is some evidence that consumption of MCTs may increase satiety, decrease energy intake, and increase energy expenditure, resulting in lower body weight and smaller fat depots compared to isocaloric LCT consumption. However, results from human studies are conflicting. High intakes of MCTs lead to reduced energy intakes in some studies at doses of 18-60 g/day, but no effects on appetite, request for food or changes in any satiety-related hormone have been observed at these intake levels. Similarly, increased energy expenditure following consumption of MCTs at high doses (15-50 g/day) has been observed in the short-term (7 days), whereas results for longer periods of time are inconsistent. No effects of MCTs at lower doses of intake (about 10 g/day) have been observed on any of these variables. The Panel considers that the evidence provided for a mechanism by which MCTs could exert the claimed effect is weak and not convincing.

In weighing the evidence, the Panel took into account that the results from the human intervention studies provided are inconsistent with respect to the effects of MCTs on body weight loss, and that the evidence in support of a mechanism by which MCTs could exert the claimed effect is weak and not convincing.

The Panel concludes that a cause and effect relationship has not been established between the consumption of MCTs and reduction in body weight.

CONCLUSIONS

On the basis of the data presented, the Panel concludes that:

- The food constituent that is the subject of the health claims is medium-chain triglycerides (MCTs). It is assumed that the food constituent which is the subject of the health claims is medium-chain fatty acids (MCFAs), which should replace long-chain fatty acids (LCFAs) in triglycerides in order to obtain the claimed effect. The food constituent, MCTs, which is the subject of the health claims, is sufficiently characterised in relation to the claimed effect.

- The claimed effect is "weight management". The target population is assumed to be overweight individuals in the general population who wish to reduce their body weight. Reduction in body weight is a beneficial physiological effect.

- A cause and effect relationship has not been established between the consumption of MCTs and reduction in body weight.

DOCUMENTATION PROVIDED TO EFSA

Health claims pursuant to Article 13 of Regulation (EC) No 1924/2006 (No: EFSA-Q-2008-1430, EFSA-Q-2008-1464, EFSA-Q-2008-2350). The scientific substantiation is based on the information provided by the Member States in the consolidated list of Article 13 health claims and references that EFSA has received from Member States or directly from stakeholders.

The full list of supporting references as provided to EFSA is available on: http://www.efsa.europa.eu/panels/nda/claims/article13.htm.

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APPENDICES

APPENDIX A

BACKGROUND AND TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

The Regulation 1924/2006 on nutrition and health claims made on foods[6] (hereinafter "the Regulation") entered into force on 19th January 2007.

Article 13 of the Regulation foresees that the Commission shall adopt a Community list of permitted health claims other than those referring to the reduction of disease risk and to children's development and health. This Community list shall be adopted through the Regulatory Committee procedure and following consultation of the European Food Safety Authority (EFSA).

Health claims are defined as "any claim that states, suggests or implies that a relationship exists between a food category, a food or one of its constituents and health".

In accordance with Article 13 (1) health claims other than those referring to the reduction of disease risk and to children's development and health are health claims describing or referring to:

a) the role of a nutrient or other substance in growth, development and the functions of the body; or

b) psychological and behavioural functions; or

c) without prejudice to Directive 96/8/EC, slimming or weight-control or a reduction in the sense of hunger or an increase in the sense of satiety or to the reduction of the available energy from the diet.

To be included in the Community list of permitted health claims, the claims shall be:

(i) based on generally accepted scientific evidence; and

(ii) well understood by the average consumer.

Member States provided the Commission with lists of claims as referred to in Article 13 (1) by 31 January 2008 accompanied by the conditions applying to them and by references to the relevant scientific justification. These lists have been consolidated into the list which forms the basis for the EFSA consultation in accordance with Article 13 (3).

ISSUES THAT NEED TO BE CONSIDERED

IMPORTANCE AND PERTINENCE OF THE FOOD[7]

Foods are commonly involved in many different functions[8] of the body, and for one single food many health claims may therefore be scientifically true. Therefore, the relative importance of food e.g. nutrients in relation to other nutrients for the expressed beneficial effect should be considered: for functions affected by a large number of dietary factors it should be considered whether a reference to a single food is scientifically pertinent.

[6] OJ L12, 18/01/2007
[7] The term 'food' when used in this Terms of Reference refers to a food constituent, the food or the food category.
[8] The term 'function' when used in this Terms of Reference refers to health claims in Article 13(1)(a), (b) and (c).

It should also be considered if the information on the characteristics of the food contains aspects pertinent to the beneficial effect.

SUBSTANTIATION OF CLAIMS BY GENERALLY ACCEPTABLE SCIENTIFIC EVIDENCE

Scientific substantiation is the main aspect to be taken into account to authorise health claims. Claims should be scientifically substantiated by taking into account the totality of the available scientific data, and by weighing the evidence, and shall demonstrate the extent to which:

(a) the claimed effect of the food is beneficial for human health,

(b) a cause and effect relationship is established between consumption of the food and the claimed effect in humans (such as: the strength, consistency, specificity, dose-response, and biological plausibility of the relationship),

(c) the quantity of the food and pattern of consumption required to obtain the claimed effect could reasonably be achieved as part of a balanced diet,

(d) the specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended.

EFSA has mentioned in its scientific and technical guidance for the preparation and presentation of the application for authorisation of health claims consistent criteria for the potential sources of scientific data. Such sources may not be available for all health claims. Nevertheless it will be relevant and important that EFSA comments on the availability and quality of such data in order to allow the regulator to judge and make a risk management decision about the acceptability of health claims included in the submitted list.

The scientific evidence about the role of a food on a nutritional or physiological function is not enough to justify the claim. The beneficial effect of the dietary intake has also to be demonstrated. Moreover, the beneficial effect should be significant i.e. satisfactorily demonstrate to beneficially affect identified functions in the body in a way which is relevant to health. Although an appreciation of the beneficial effect in relation to the nutritional status of the European population may be of interest, the presence or absence of the actual need for a nutrient or other substance with nutritional or physiological effect for that population should not, however, condition such considerations.

Different types of effects can be claimed. Claims referring to the maintenance of a function may be distinct from claims referring to the improvement of a function. EFSA may wish to comment whether such different claims comply with the criteria laid down in the Regulation.

WORDING OF HEALTH CLAIMS

Scientific substantiation of health claims is the main aspect on which EFSA's opinion is requested. However, the wording of health claims should also be commented by EFSA in its opinion.

There is potentially a plethora of expressions that may be used to convey the relationship between the food and the function. This may be due to commercial practices, consumer perception and linguistic or cultural differences across the EU. Nevertheless, the wording used to make health claims should be truthful, clear, reliable and useful to the consumer in choosing a healthy diet.

In addition to fulfilling the general principles and conditions of the Regulation laid down in Article 3 and 5, Article 13(1)(a) stipulates that health claims shall describe or refer to "the role of a nutrient or other substance in growth, development and the functions of the body". Therefore, the requirement to

describe or refer to the 'role' of a nutrient or substance in growth, development and the functions of the body should be carefully considered.

The specificity of the wording is very important. Health claims such as "Substance X supports the function of the joints" may not sufficiently do so, whereas a claim such as "Substance X helps maintain the flexibility of the joints" would. In the first example of a claim it is unclear which of the various functions of the joints is described or referred to contrary to the latter example which specifies this by using the word "flexibility".

The clarity of the wording is very important. The guiding principle should be that the description or reference to the role of the nutrient or other substance shall be clear and unambiguous and therefore be specified to the extent possible i.e. descriptive words/ terms which can have multiple meanings should be avoided. To this end, wordings like "strengthens your natural defences" or "contain antioxidants" should be considered as well as "may" or "might" as opposed to words like "contributes", "aids" or "helps".

In addition, for functions affected by a large number of dietary factors it should be considered whether wordings such as "indispensable", "necessary", "essential" and "important" reflects the strength of the scientific evidence.

Similar alternative wordings as mentioned above are used for claims relating to different relationships between the various foods and health. It is not the intention of the regulator to adopt a detailed and rigid list of claims where all possible wordings for the different claims are approved. Therefore, it is not required that EFSA comments on each individual wording for each claim unless the wording is strictly pertinent to a specific claim. It would be appreciated though that EFSA may consider and comment generally on such elements relating to wording to ensure the compliance with the criteria laid down in the Regulation.

In doing so the explanation provided for in recital 16 of the Regulation on the notion of the average consumer should be recalled. In addition, such assessment should take into account the particular perspective and/or knowledge in the target group of the claim, if such is indicated or implied.

TERMS OF REFERENCE

HEALTH CLAIMS OTHER THAN THOSE REFERRING TO THE REDUCTION OF DISEASE RISK AND TO CHILDREN'S DEVELOPMENT AND HEALTH

EFSA should in particular consider, and provide advice on the following aspects:

- Whether adequate information is provided on the characteristics of the food pertinent to the beneficial effect.
- Whether the beneficial effect of the food on the function is substantiated by generally accepted scientific evidence by taking into account the totality of the available scientific data, and by weighing the evidence. In this context EFSA is invited to comment on the nature and quality of the totality of the evidence provided according to consistent criteria.
- The specific importance of the food for the claimed effect. For functions affected by a large number of dietary factors whether a reference to a single food is scientifically pertinent.

In addition, EFSA should consider the claimed effect on the function, and provide advice on the extent to which:

- the claimed effect of the food in the identified function is beneficial.
- a cause and effect relationship has been established between consumption of the food and the claimed effect in humans and whether the magnitude of the effect is related to the quantity

consumed.

- where appropriate, the effect on the function is significant in relation to the quantity of the food proposed to be consumed and if this quantity could reasonably be consumed as part of a balanced diet.
- the specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended.
- the wordings used to express the claimed effect reflect the scientific evidence and complies with the criteria laid down in the Regulation.

When considering these elements EFSA should also provide advice, when appropriate:

- on the appropriate application of Article 10 (2) (c) and (d) in the Regulation, which provides for additional labelling requirements addressed to persons who should avoid using the food; and/or warnings for products that are likely to present a health risk if consumed to excess.

APPENDIX B

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of the food/food constituent, a positive assessment of its safety, nor a decision on whether the food/food constituent is, or is not, classified as foodstuffs. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope, the proposed wordings of the claims and the conditions of use as proposed in the Consolidated List may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 13(3) of Regulation (EC) No 1924/2006.

APPENDIX C

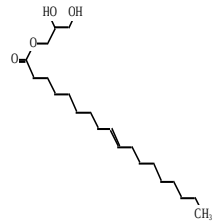
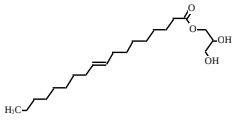
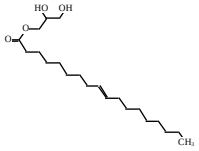
Table 1. Main entry health claims related to medium-chain triglycerides, including conditions of use from similar claims, as proposed in the Consolidated List.

ID	Food or Food constituent	Health Relationship	Proposed wording
643	medium chain triglycerides (MCT)	weight management	- helps to manage body weight, - helps to reduce body fat particularly in overweight persons, - helps to limit body fat accumulation, - helps to increase energy expenditure.
	Conditions of use - 5g/day - from 2g to 10g/day		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
677	Medium Chain Triglycerides; MCT;	Weight management	Consumption of Medium Chain Triglycerides (MCT) inside the normal suggested fat consumption contributes to keep the healthy balanced body weight and helps to avoid fat deposition, with special regards to the abdominal fat.;;MCT helps to increase energy expenditure in comparison to the long chain fatty acides by increasing the metabolic rate.
	Conditions of use - 30-40 g/day short term use; 5 g/day;long term use		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
1614	Medium Chain Triglycerides (MCT)	Weight management	Helps to increase satiety after a meal /helps to increase energy expenditure by increasing the metabolic rate /helps with weight loss by increasing metabolic rate /tends to reduce body weight and fat in overweight persons
	Conditions of use - 5g/day - 30-40 g/day short term use; 5 g/day;long term use - kurzfristig 30-40 g/Tag, langfristig 10 g/Tag - from 2g to 10g/day - 30-40 g/day short term use. 10 g/d long term use		

GLOSSARY AND ABBREVIATIONS

BMI	Body mass index
LCFA	Long-chain fatty acid
LCPUFA	Long-chain polyunsaturated fatty acid
LCSFA	Long-chain saturated fatty acid
LCT	Long-chain triglyceride
MCT	Medium-chain triglyceride
MLCT	Medium and long-chain triglycerides
VLCD	Very low calorie diet

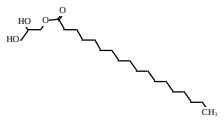
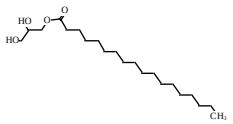
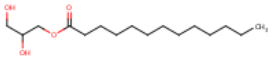
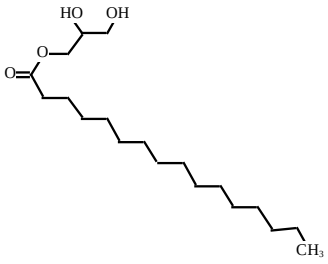
SIDS INITIAL ASSESSMENT PROFILE

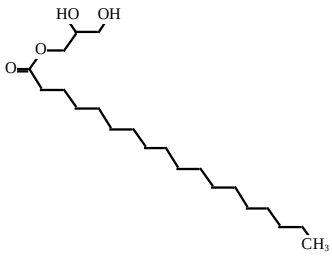
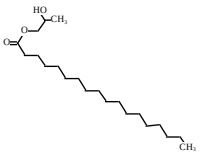
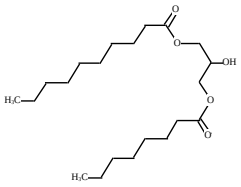
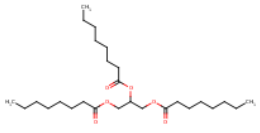
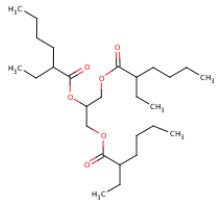
Category name	Glycerides Category		
CAS No(s), Chemical name(s) and structural formula(s) [1]	**CAS No [Class** [2] **]**	**IUPAC or CAS Name**	**Structural Formula**
	Monoglycerides		
	25496-72-4 [2]	Olein, mono-Octadecenoic acid, 1,2,3-propanetriol	
	37220-82-9 [2]	Glycerol oleate	
	68309-32-0 and 61790-12-3 [3] **[2]**	Glycerides,tall-oil	

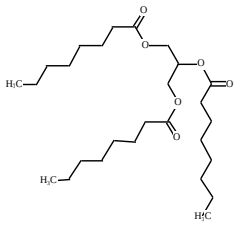
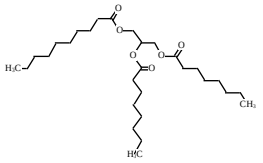
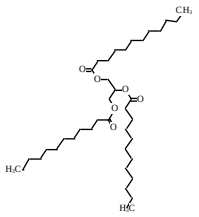
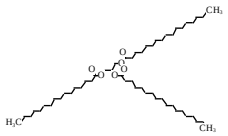
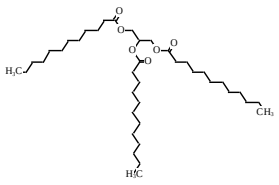
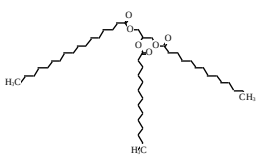
[1] Glycerides are commonly identified by industry and regulatory authorities as mono-, di-, tri, etc. and therefore the logical way to group the information in a manner that makes sense to the reader/reviewer is to provide subcategories (monoglycerides, diglycerides, triglycerides and mixtures of mono-, di- and triglycerides) and is consistent with the way these compounds are referenced in literature and regulatory references.

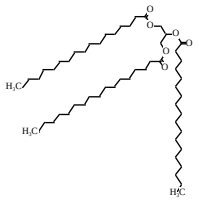
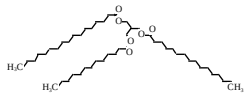
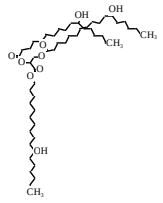
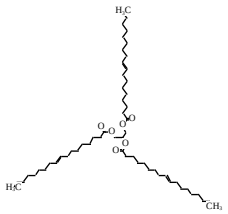
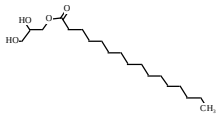
[2] Class 1 = single compounds composed of molecules with particular atoms arranged in a definite, known structure.
Class 2 = CHEMICAL SUBSTANCES OF UNKNOWN OR VARIABLE COMPOSITION, COMPLEX REACTION PRODUCTS AND BIOLOGICAL MATERIALS (UVCB)

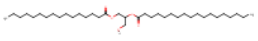
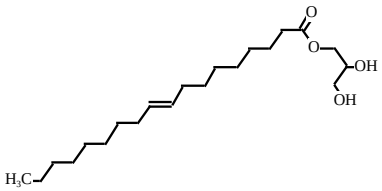
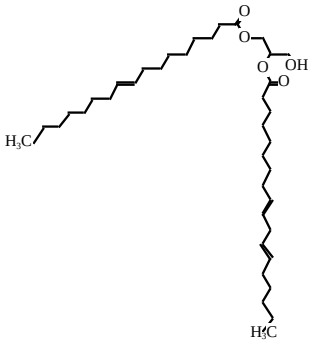
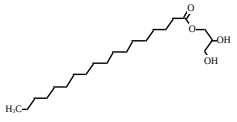
[3] The substances are analogues (the two CAS numbers describe the same substance).

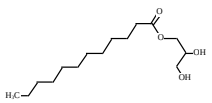
	31566-31-1 [2]	Octadecanoic acid, monoester with 1,2,3-propanetriol	
	61789-09-1 [2]	Monoglycerides, hydrogenated tallow	
	11099-07-3 and 67701-27-3[3] [2]	Glyceryl stearate	 and 
	91744-73-9 [2]	Glycerides, palm-oil mono-, hydrogenated	 and

		
	Diglycerides	
1323-39-3 **[2]**	Octadecanoic acid, 1,2-propanediol monoester	
65381-09-1 **[2]**	Decanoic acid, ester with 1,2,3-propanetriol octanoate	
	Triglycerides	
538-23-8 **[1]**	Octanoin, tri- (Octanoic acid, 1,2,3-propanetriyl ester; Tricaprylin)	
7360-38-5 **[1]**	Hexanoic acid, 2-ethyl-, 1,2,3-propanetriyl ester	

	85409-09-2 **[2]**	Glycerides, C8-10	
	73398-61-5 **[2]**	Glycerides, mixed decanoyl and octanoyl	
	8023-79-8 **[2]**	Oils, glyceridic, palm kernel	
	67701-28-4 **[2]**	Glycerides, C8-18 and C18-unsatd.	
	68334-28-1 **[2]**	Oils, vegetable, hydrogenated	
	67701-26-2 **[2]**	Glycerides, C12-18 (C14:C14:C18)	

	67701-30-8 **[2]**	Glycerides, C16-18 and C18-unsatd. (C18:C18:C18)	
	8030-12-4 **[2]**	Tallow, hydrogenated	
	8001-78-3 **[2]**	Castor oil, hydrogenated	
	122-32-7 **[2]**	Olein, tri - (Octadecenoic acid, 1,2,3-propanetriyl)	
	Mixtures of mono-, di- and triglycerides[1]		
	67701-33-1 **[2]**	Glycerides, C14-18 mono- and di-	
	68606-18-8 **[2]**	Glycerides, mixed coco, decanoyl and octanoyl	UVCB
	68424-61-3 **[2]**	Glycerides, C16-18 and C18-unsatd. mono- and di-	UVCB

	85251-77-0 [2]	Glycerides, C16-18 mono- and di-	
	97722-02-6 [2]	Glycerides, tall-oil mono-, di-, and tri-	 and 
	91744-20-6 [2]	Glycerides, C16-18 and C18-unsatd. mono-, di- and tri-	

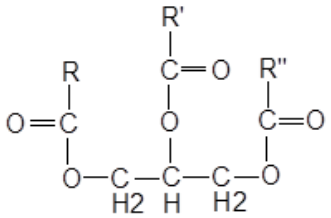
	68991-68-4 and **91052-53-8**[3] **[2]**	Coconut oil, transesterification products with decanoic acid mixed ester with glyceryl octanoate	

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

The Glyceride Category contains thirty-one (31) sponsored glyceride substances which are defined as esters of monocarboxylic acids and glycerol bearing one (monoglycerides), two (diglycerides) or three (triglycerides) aliphatic chains, or, a mixture of mono-, di- and triglycerides, each ranging in number of carbons from 8 to 18. The C18 members of the group may be saturated or unsaturated with one carbon-carbon double bond. The glycerides grouping consists of both discrete chemicals with an incremental and constant change across its members (carbon chain length) and commercial mixtures that are composed of glycerides with a range of carbon chain lengths in its aliphatic side groups. The carbon chains do not contain any branching (they are all straight chains).

The chemical structure of the triglyceride members of this Glyceride Category is:



R, R1, and R2 are aliphatic chains containing from 8-18 carbon atoms, and two or three chains may be identical. The monoglycerides and diglycerides in this Glyceride Category have a similar structure except that glycerol is bonded to one and two aliphatic (fatty acid) chains, respectively, and have two and one free hydroxyl groups, respectively.

Glycerides are a group of lipids commonly called fats (solid at room temperature) and oils (liquid at room temperature). Due to the structural similarities of the glycerides, their physico-chemical properties are similar and

a clear correlation with chain length is observed. Melting point and boiling point increase with increasing chain length. The vapor pressures of the glycerides decrease with increasing carbon number and generally are low. Water solubility decreases and partition coefficient between octanol and water increase with increasing carbon number.

Fatty acids are generally ingested as triglycerides, which cannot be absorbed by the small intestine. When ingested, monoglycerides are readily absorbed through the duodenal mucosa and converted to triglycerides. In the small intestine, most triglycerides are split by pancreatic lipases into monoglycerides, free fatty acids, and glycerol, which can be absorbed by the intestinal mucosa. A small fraction of triglycerides are absorbed as free glycerol and as diglycerides. Once across the intestinal barrier, triglycerides are reformed. These resynthesized triglycerides collect into globules along with cholesterol and phospholipids and are encased in a protein coat as chylomicrons. Chylomicrons are transported in the lymph to the thoracic duct and eventually to the venous system. The chylomicrons are removed from the blood as they pass through the capillaries of adipose tissue. Fat is stored in adipose cells until it is transported to other tissues as free fatty acids which are used for cellular energy or incorporated into cell membranes.

Based on similarities in structural, physical chemical and toxicokinetic properties, read across among the sponsored substances is reasonable. The following table presents a summary of the read across approach (**bold text** indicates data are available; Read across is designated as "RA"). Read across results were selected based on the lowest available effects value or most conservative result.

Substance CAS#	**Acute toxicity (oral and inhalation)**	**Repeated dose (oral)**	**Gene mutation *in vitro***	**Chromosome aberration *in vitro***	**Chromosome aberration *in vivo***	**Effects on fertility and reproductive organs**	**Developmental toxicity (oral)**
Monoglycerides							
Olein, mono-Octadecenoic acid, 1,2,3-propanetriol **25496-72-4**	LD50 oral >2,000 (Read across (RA)	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Glycerol oleate **37220-82-9**	LD50 oral >2,000 (RA)	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Glycerides,tall-oil **68309-32-0** and **61790-12-3**	**LD50 oral >10,000**	**NOAEL = 12,500 (90 day)**	**Negative**	**Negative**	Negative (RA)	**NOAEL = 5000 (M/F)**	**NOAEL = 5000**
Octadecanoic acid, monoester with 1,2,3-propanetriol **31566-31-1**	LD50 oral >2,000 (RA)	NOAEL = 2500 (90 day) (RA)	**Negative**	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Monoglycerides, hydrogenated tallow **61789-09-1**	LD50 oral >2,000 (RA)	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Glyceryl stearate **11099-07-3** and **67701-27-3**	**LD50 oral >5,000**	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Diglycerides							
Octadecanoic acid, 1,2-propanediol monoester **1323-39-3**	**LD50 oral >5,000**	**NOAEL = 3760 (13 week)**	Negative (RA)	Negative (RA)	Negative (RA)	**NOAEL = 3760 (M/F)**	NOAEL = 5000 (RA)
Decanoic acid, ester with 1,2,3-propanetriol octanoate **65381-09-1**	**LD50 oral >5,000**	**NOAEL = 2500 (90 day)**	Negative (RA)	Negative (RA)	Negative (RA)	**NOAEL = 9800 (M/F)**	NOAEL = 5000 (RA)
Triglycerides							
Octanoin, tri-(Octanoic acid, 1,2,3-propanetriyl ester; Tricaprylin) **538-23-8**	**LD50 oral >5,000**	**NOAEL = 9500 (26 week)**	**Negative**	Negative (RA)	**Negative**	NOAEL = 5000 (M/F) (RA)	**NOAEL = 9500 (M/F)**

Hexanoic acid, 2-ethyl-, 1,2,3-propanetriyl ester **7360-38-5**	**LD50 oral >48,000**	NOAEL = 2500 (90 day) (RA)	**Positive**	Negative (RA)	**Negative**	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Glycerides, C8-10 **85409-09-2**	**LD50 oral >2,500**	**NOAEL = 2500 (90 day)**	Negative (RA)	Negative (RA)	Negative (RA)	**NOAEL = 9800 (M/F)**	NOAEL = 5000 (RA)
Glycerides, mixed decanoyl and octanoyl **73398-61-5**	**LD50 oral >5,000**	**NOAEL = 2500 (90 day)**	**Negative**	Negative (RA)	Negative (RA)	**NOAEL = 9800 (M/F)**	NOAEL = 5000 (RA)
Oils, glyceridic, palm kernel **8023-79-8**	**LD50 oral >5,000**	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	**NOAEL = 5000 (M/F)**	**NOAEL = 5000 (M/F)**
Glycerides, C8-18 and C18-unsatd. **67701-28-4**	LD50 oral >2,000 (RA)	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Oils, vegetable, hydrogenated **68334-28-1**	LD50 oral >2,000 (RA)	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Glycerides, C12-18 **67701-26-2**	**LD50 oral >10,000**	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Glycerides, C16-18 and C18-unsatd. **67701-30-8**	LD50 oral >2,000 (RA)	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Tallow, hydrogenated **8030-12-4**	LD50 oral >2,000 (RA)	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Castor oil, hydrogenated **8001-78-3**	LD50 oral >2,000 (RA)	NOAEL = 2500 (90 day) (RA)	**Negative**	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Olein, tri - (Octadecenoic acid, 1,2,3-propanetriyl) **122-32-7**	**LD50 oral >2,000**	NOAEL = 2500 (90 day) (RA)	**Negative**	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Mixtures of mono-, di- and triglycerides							
Glycerides, C14-18 mono- and di- **67701-33-1**	LD50 oral >2,000 (RA)	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Glycerides, mixed coco, decanoyl and octanoyl **68606-18-8**	LD50 oral >2,000 (RA)	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Glycerides, C16-18 mono- and di- **85251-77-0**	LD50 oral >2,000 (RA)	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Glycerides, tall-oil mono-, di-, and tri- **97722-02-6**	LD50 oral >2,000 (RA)	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Glycerides, C16-18 and C18-unsatd. mono-, di- and tri- **91744-20-6**	**LD50 oral >2,000**	NOAEL = 2500 (90 day) (RA)	**Negative**	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)
Coconut oil,transesterification products with decanoic acid mixed ester with glyceryl octanoate **68991-68-4** and **91052-53-8**	LD50 oral >2,000 (RA)	NOAEL = 2500 (90 day) (RA)	Negative (RA)	Negative (RA)	Negative (RA)	NOAEL = 5000 (M/F) (RA)	NOAEL = 5000 (RA)

Substance CAS#	Biodegradation	Acute aquatic toxicity (mg/L)		
		Fish 96 hr LC50	Aquatic invertebrate 48 hr EC50	Aquatic plants 72 hr EC50
Monoglycerides				
Olein, mono- Octadecenoic acid, 1,2,3-propanetriol **25496-72-4**	Readily biodegradable (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Glycerol oleate **37220-82-9**	Readily biodegradable (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Glycerides,tall-oil **68309-32-0** and **61790-12-3**	**Readily biodegradable**	**LL50* >1000 (nominal)**	**EL50* >1000 (nominal)**	**EbL50* = 854.9 (nominal), ErL50* >1000 (nominal)**
Octadecanoic acid, monoester with 1,2,3-propanetriol **31566-31-1**	**Readily biodegradable**	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Monoglycerides, hydrogenated tallow **61789-09-1**	Readily biodegradable (RA)	**>10,000 (nominal)**	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Glyceryl stearate **11099-07-3** and **67701-27-3**	Readily biodegradable (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Diglycerides				
Octadecanoic acid, 1,2-propanediol monoester **1323-39-3**	Readily biodegradable (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Decanoic acid, ester with 1,2,3-propanetriol octanoate **65381-09-1**	**Readily biodegradable**	**>10,000 (nominal)**	**EL50 >100 (nominal; 21 d)**	**EbL50, ErL50 >100 (nominal)**
Triglycerides				
Octanoin, tri- (Octanoic acid, 1,2,3-propanetriyl ester; Tricaprylin) **538-23-8**	Readily biodegradable (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Hexanoic acid, 2-ethyl-, 1,2,3-propanetriyl ester **7360-38-5**	**Readily biodegradable**	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Glycerides, C8-10 **85409-09-2**	**Readily biodegradable**	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Glycerides, mixed decanoyl and octanoyl **73398-61-5**	**Readily biodegradable**	**>53 (measured)**	**EL50 >100 (nominal)**	**EbL50, LLr50 > 1000 (nominal)**
Oils, glyceridic, palm kernel **8023-79-8**	Readily biodegradable (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Glycerides, C8-18 and C18-unsatd. **67701-28-4**	Readily biodegradable (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Oils, vegetable, hydrogenated **68334-28-1**	Readily biodegradable (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Glycerides, C12-18 **67701-26-2**	Readily biodegradable (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Glycerides, C16-18 and C18-unsatd. **67701-30-8**	**Readily biodegradable**	**>10,000 (nominal)**	**EL50 >100 (nominal; 21 d)**	**EbL50, ErL50 >100 (nominal)**
Tallow, hydrogenated **8030-12-4**	Readily biodegradable (RA)	>100 or exceeds water solubility (RA)	**EL50 >100 (nominal)**	**EbL50, ErL50 >100 (nominal)**
Castor oil, hydrogenated **8001-78-3**	**Readily biodegradable**	**>10,000 (nominal)**	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Olein, tri - (Octadecenoic acid, 1,2,3-propanetriyl) **122-32-7**	**Readily biodegradable**	>100 or exceeds water solubility (RA)	**EL50 >100 (nominal)**	>100 or exceeds water solubility (RA)
Mixtures of mono-, di- and triglycerides				
Glycerides, C14-18 mono- and di- **67701-33-1**	**Readily biodegradable**	**>10,000 (nominal)**	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Glycerides, mixed coco, decanoyl and octanoyl **68606-18-8**	Readily biodegradable (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Glycerides, C16-18 mono- and di- **85251-77-0**	Readily biodegradable (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)

Glycerides, tall-oil mono-, di-, and tri- **97722-02-6**	**Readily biodegradable**	**1700 (nominal)**	**EL50 >100 (nominal)**	**ECr50 = 13.88 (nominal; exceeds the estimated water solubility of the substance)**
Glycerides, C16-18 and C18-unsatd. mono-, di- and tri- **91744-20-6**	**Readily biodegradable**	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)
Coconut oil,transesterification products with decanoic acid mixed ester with glyceryl octanoate **68991-68-4** and **91052-53-8**	Readily biodegradable (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)	>100 or exceeds water solubility (RA)

*WAF sample preparations are reported relative to a loading rate rather than a concentration [LL50 (fish); EL50 (daphnia); EbL50/ErL50 (algae)]

Physical-chemical Properties

The thirty-one (31) sponsored substances are solid or liquid glycerides and include i) two (2) substances composed of molecules with particular atoms arranged in a definite, known structure (defined chain length), and ii) twenty-nine (29) substances that are mixtures with a range of components. It is not possible to estimate values for mixtures with confidence and for the purposes of this assessment have been characterized by a representative chain length.

A property of a mixture of glycerides is therefore a function of that property for each of the discrete chain length components in the mixture. Melting point and boiling point increase with increasing chain length. Measured melting point values range from -32°C (**CAS 122-32-7;** triglyceride) to 85.4 °C (**CAS 8001-78-3,** triglyceride); for glycerides without measured data, estimated melting points range from 57-74 °C (**CAS 91744-20-6,** monoglyceride) to 349.8 °C (**CAS 67701-30-8,** triglyceride). Measured boiling point values range from 233°C at 1013 hPa (**CAS 538-23-8,** triglyceride) to 360-410 °C at 1013-1021 hPa (**CAS 7360-38-5,** triglyceride); for glycerides without measured data, estimated boiling points range from 378.7 °C (**CAS 68991-68-4 and 91052-53-8,** Mixtures of mono-, di- and triglycerides) to 893.4 °C (**CAS 8001-78-3,** triglyceride). Vapor pressure decreases with increasing carbon number and generally are low (5.09E-10 hPa at 25°C for **CAS 538-23-8,** triglyceride**,** measured; for glycerides without measured data, estimated values are <1E-05 hPa. Water solubility increases with decreasing carbon number; measured values range from <0.05 mg/L at 20°C (**CAS 8001-78-3**) to 3020 mg/L at 20 °C (**CAS 7360-38-5**, triglyceride); for glycerides without measured data, estimated values range from 6.52E-21 mg/L (**CAS 67701-30-8,** triglyceride) to 12.7 mg/L (**CAS 68991-68-4 and 91052-53-8,** Mixtures of mono-, di- and triglycerides). Measured partition coefficient values (log Kow) range from >3 at 20°C (**CAS 73398-61-5,** triglyceride) to >6.5 (**CAS 7360-38-5,** triglyceride); for glycerides without measured data, estimated values range from 3.7 (**CAS 68991-68-4 and 91052-53-8,** Mixtures of mono-, di- and triglycerides) to 23.9 (**CAS 67701-30-8,** triglyceride).

Human Health

Most of the available toxicokinetic data (animal and humans) relates to the absorption of triglycerides including **CAS 122-32-7**, **CAS 7360-38-5**, **CAS 8023-79-8** and **CAS 73398-61-5**, following oral administration, with limited data on its absorption after intravenous and dermal dosing. Toxicokinetic data are also available for **CAS 1323-39-3** (diglyceride), Data were not located for the inhalation route.

Glycerides are expected to be readily absorbed following ingestion, with rapid elimination from most tissues (possible exception of adipose, spleen). Glyceride metabolism and re-synthesis play a role in the absorption and distribution of ingested glycerides. Expiration is at least one route of elimination for ingested glycerides. These pathways are relevant for humans as well as other mammals.

Acute oral toxicity studies were located for twelve (12) Glyceride Category members (CAS **61790-12-3 and 11099-07-3** (monoglycerides)**, 1323-39-3 and 65381-09-1** (diglycerides)**, 538-23-8, 7360-38-5, 85409-09-2, 73398-61-5, 8023-79-8, 67701-26-2 and 122-32-7** (triglycerides) and, **91744-20-6** (mixtures of mono-, di- and triglycerides)). The oral LD50s for rats are > 2000 mg/kg bw (**CAS 122-32-7** (triglycerides) and **91744-20-6** (mixtures of mono-, di- and triglycerides)), and range up to > 48,000 mg/kg bw (**CAS 7360-38-5** (triglyceride) (OECD 401, Directive 84/449/EEC, B.1, or no guideline specified)). At doses consistent with recent testing standards (i.e., 2000 to 5000 mg/kg bw), there were no clinical signs, changes in body weight or findings at gross necropsy. Similar findings (LD50s and lack of toxicity) were reported for mice. Acute aerosol inhalation studies

were located for two glycerides (**CAS 85409-09-2** and **73398-61-5,** triglycerides); there were no adverse findings when rats or guinea pigs were exposed to 0.028 mg/L for six hours.

Skin and eye irritation studies were located for six (6) and five (5) members of the Glycerides Category, respectively. The Glycerides (**CAS 11099-07-3** (monoglyceride), **1323-39-3** (diglyceride), **7360-38-5, 73398-61-5** and **8023-79-8** (triglycerides) and **91744-20-6** (mixtures of mono-, di- and triglycerides) are not irritating to slightly irritating to the skin in standard irritation (Draize, OECD 405, FHSLA, or DOT) studies using rabbits. When a single occlusive patch containing an undiluted glyceride (**CAS 11099-07-3,** monoglyceride) was applied to human volunteer skin for 24 hours, no to slight irritation was noted. The Glycerides (**CAS 11099-07-3 (**monoglyceride**), 1323-39-3 (**diglyceride**), 73398-61-5** and **67701-26-2** (triglycerides) and **91744-20-6 (**mixtures of mono-, di- and triglycerides)) are not irritating to slightly irritating to the eyes in standard eye irritation (Draize or similar) studies using rabbits. The untested members of the Glyceride Category are expected to be not or slightly irritating to the skin and eyes. Clinical signs of respiratory tract irritation were not observed following 6 hour inhalation exposures to aerosols of two Glyceride Category members (**CAS 85409-09-2** and **73398-61-5,** triglycerides**)** at 0.028 mg/L.

Skin sensitization studies with guinea pigs and/or human volunteers were located for four (4) members of the Glycerides Category. In standard Magnusson and Kligman guinea pig maximization tests, the Glyceride Category members were not skin sensitizers. **CAS 73398-61-5,** triglyceride) was tested only in a guinea pig maximization test). In patch **(CAS 11099-07-3,** monoglyceride, and **7360-38-5,** triglyceride) or chamber studies with human volunteers (**CAS 122-32-7**, triglyceride), the Glyceride Category members were not skin sensitizers. The untested members of the Glyceride Category are expected to also not be skin sensitizers.

Repeated dose oral (gavage or diet studies) have been located for six (6) of the Glyceride Category members (**CAS 61790-12-3 (**monoglyceride**), 1323-39-3** and **65381-09-1 (**diglycerides**), 538-23-8, 85409-09-2** and **73398-61-5** (triglycerides). There were no adverse effects of treatment reported following repeated oral studies with rats, by either gavage or diet route. The NOAELs were =>2500 mg/kg bw, indicating the Glyceride Category members are not toxic. Although the studies do not conform to current, standard guidelines, the substances do not cause systemic toxicity. Similar results are expected for the Glyceride Category members that have not been tested.

In vitro and *in vivo* mutagenicity studies have been located for eight (8) and one (1) of the Glyceride Category members, respectively. The Glyceride Category members are negative for genotoxicity (*in vitro* bacterial reverse mutation assays (**CAS 68309-32-0** and **61790-12-3** and **31566-31-1 (**monoglycerides**), 538-23-8**, **73398-61-5, 8001-78-3** and **122-32-7 (**triglycerides**),** and **91744-20-6 (**mixtures of mono-, di- and triglycerides), *in vivo* host-mediated mutagenicity assay (**CAS 538-23-8,** triglyceride), in vitro (**CAS 68309-32-0** and **61790-12-3**, monoglycerides) or *in vivo* (**CAS 538-23-8,** triglyceride) chromosomal aberration, in vivo micronucleus assay (**CAS 538-23-8,** triglyceride), *in vivo* dominant lethal (**CAS 538-23-8**, triglyceride) and SCE (**CAS 538-23-8,** triglyceride and **CAS 7360-38-5**, triglyceride). One of the substances (CAS **7360-38-5**, triglyceride), was positive in an *in vivo* mouse spot test; the weight of evidence suggests this is not representative of the Glyceride Category members. A lack of genotoxicity is expected for those Glyceride Category members that have not been tested.

A carcinogenicity study has been located for Glyceride Category member **CAS 538-23-8 (**triglyceride**)**. In a two year gavage carcinogenicity study, there were significant dose-related increased incidences of pancreatic exocrine hyperplasia and adenoma, and proliferative lesions of the forestomach of rats administered **CAS 538-23-8 (**triglyceride**)**. Nephropathy and related severity were significantly decreased in high dose rats, and the incidence of mononuclear cell leukemia was decreased. A level of evidence of carcinogenicity was not assigned by NTP. A carcinogenicity study with tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) was conducted to test the transplacental carcinogenicity of NNK. Groups of pregnant hamsters were given subcutaneous (s.c.) injections of single or multiple doses of NNK (cumulative dose range, 50–300 mg/kg**),** on day 15 (last day of gestation) or on days 13, 14, and 15 of gestation, three s.c. injections of **CAS 7360-38-5** (triglyceride, 43 males, 40 females, last 3 days of gestation) and the offspring were evaluated for tumor development up to one year later. Within 1 year after treatment, up to 70% of the offspring developed tumors in various organs, including respiratory tract, nasal cavity, adrenal glands, pancreas, and liver. No tumors were found in the control hamsters treated with the vehicle (trioctanoin) alone. The overall tumor incidence was proportional to the cumulative dose. Females had a generally higher tumor incidence than males. **CAS 7360-38-5** (triglyceride) was negative in this study for transplacental carcinogenicity.

Effects on fertility and developmental toxicity studies were located for six (6) and five (5) Glyceride Category members, respectively. There were no effects on fertility (**CAS 61790-12-3** (monoglyceride)**, 1323-39-3** and **65381-09-1** (diglycerides), **85409-09-2, 73398-61-5** and **8023-79-8** (triglycerides**)** or developmental effects (**CAS 61790-12-3**, monoglyceride, **538-23-8, 7360-38-5** and **8023-79-8,** triglycerides**)** in rats, mice or hamsters in studies similar to OECD 416, FDA/WHO/DGHS safety evaluation protocol, 90 day studies examining reproductive organs, three–generation study or developmental studies with no protocol specified. In a developmental toxicity study in rats in which **CAS 538-23-8** was used as the vehicle control (9500 mg/kg bw) and water was used as the negative control, it was evident that the vehicle itself exerted a mild degree of developmental toxicity. There was a statistically significant 8% increase in total soft tissue malformations in the vehicle control group compared to 0% in the water control group. Maternal weight gain and fetal size were also lower in animals receiving **CAS 538-23-8** compared to the water controls, but these were not statistically significant." In a 3-generation study with **CAS 73398-61-5** (triglyceride), during lactation the volume of milk secreted by rats receiving the medium chain triglyceride in the diet at 9800 mg/kg bw was smaller and resulted in slower gain in body weight; after weaning, normal growth of the rats resumed. In this study, the LOAEL for developmental toxicity was 9800 mg/kg bw. Although the studies do not all conform to current, standard guidelines, the NOAELs were all greater than 2000 mg/kg bw. Similar results are expected for the Glyceride Category members which have not been tested.

The Glycerides Category members do not possess properties indicating a hazard for human health. Adequate screening-level data are available to characterize the hazard to human health for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

Hydrolysis (OECD TG 111) studies have not been conducted for the glycerides. The ester group on the glycerides can be hydrolyzed to generate glycerin and the corresponding fatty acid. However, hydrolysis is expected to be very slow (>1 year) at room temperature, and the limited water solubility and steric hindrance of many of these substances will contribute to the lack of hydrolysis. If hydrolysis were to occur, the expected hydrolysis products (glycerin and the fatty acid) would not further hydrolyze, as there are no additional hydrolyzable groups for these substances.

The glycerides are subject to indirect photodegradation in air. Modeled photodegradation rates (half-lives) were estimated using AopWin v1.92 (EPI Suite v4.11). Estimated half-lives (hours; based on 12 hours of light per day; 1.5E+6 OH/cm^3) for hydroxyl radicals generally increase with decreasing chain length and range from ca. 0.5 hours (**CAS 122-32-7,** triglyceride) to 4.7 hours (**CAS 7360-38-5**, triglyceride). No ozone reaction was estimated for most of the glycerides (the model is only applicable to unsaturated molecules); for those Glyceride Category members for which an estimation was made, the half-lives (hours, 7E-11 mol/cm^3) for ozone reaction range from 0.46 to 2.1 hours (**CAS 25496-72-4, 37220-82-9, 68309-32-0** and **61790-12-3** (monoglycerides), **122-32-7** (triglyceride), **68424-61-3** and **97722-02-6** (mixtures of mono-, di- and triglycerides). Level III fugacity modelling using EPI Suite v4.11 indicates that the glycerides will distribute primarily to soil and water, with lesser amounts to air and sediment.

Biodegradation studies generally confirm that the extent of biodegradation observed in 28 days meets the ready biodegradability criterion (**CAS 68309-32-0** and **61790-12-3** (monoglycerides, 56-84% in 28 days)**, 31566-31-1** (monoglyceride, 108% in 51 days), **65381-09-1** (monoglyceride, 73 - 88% in 30 days), **7360-38-5** (triglyceride, >= 70.2 — <= 73.8 in 28 days), **85409-09-2** (triglyceride, 91.2 - 99.6% in 28 days), **73398-61-5** (triglyceride, 93% in 28 days), **67701-30-8** (triglyceride, 73 - 109% in 30 days)**, 8001-78-3** (triglyceride, 64% in 28 days)**, 122-32-7** (triglyceride, 77% in 28 days), **67701-33-1** (69 - 95% in 28 days; 68 - 73% in 30 days), **97722-02-6** (79% in 28 days)**,** and **91744-20-6** (mixtures of mono-, di- and triglycerides, 72% in 28 days)). In one study, biodegradation under anaerobic conditions was also demonstrated (CAS **122-32-7**; triglyceride, 63-106% in 51 days). Glyceride Category members that have not been tested are expected to be readily biodegradable based on read across to other Glyceride Category members.

Measured bioconcentration (BCF) factor data were not located for the Glycerides Category members. Estimated BCF values are calculated using BCFBAF v3.01 (EPI Suite v4.11). The Glyceride Category members have BCF values less than 500, indicating a low potential for bioaccumulation with the exception of **CAS 1323-39-3 (**diglyceride), with estimated BCF value of 1574. However, this value is very likely an overestimate of the substance's bioaccumulation potential since the influence of metabolism (via the common mechanism of β-

oxidation), which will be very high for substances in this category, is not fully represented. Overall, substances in the category have a low potential for bioaccumulation.

Due to the poorly soluble nature of many category members, it was difficult to distinguish whether the toxicity observed was due to the chemical toxicity or the physical presence of the test substance (particulates floating in and on the surface of the water, suds or film on the surface of the water) during aquatic toxicity testing. Therefore, two general strategies were used for testing these substances: (1) the use of a Water Accommodated Fraction (WAF) prepared at a maximum loading rate (i.e. concentrations of the test substance is significantly above its solubility limit) or (2) the use of a direct addition method in which the test substance was added directly to the test vessels, followed by shaking/stirring/use of a homogenizer for an extended period of time to allow for equilibrium. For both of these methods, it is more appropriate to report the nominal loading rate rather than a measured concentration, since the values greatly exceed the water solubility of the test substance. Acute toxicity test results are presented for aquatic species.

Fish

Name and CAS Number	Species/Test method	LC50 (mg/L), 96 hr	
Monoglycerides			
Olein, mono- Octadecenoic acid, 1,2,3-propanetriol **25496-72-4**	No data located		
Glycerol oleate **37220-82-9**	No data located		
Glycerides,tall-oil **68309-32-0** and **61790-12-3**	*Pimephales promelas*/ OECD 203/static	LL50* >1000 (nominal)	
Octadecanoic acid, monoester with 1,2,3-propanetriol **31566-31-1**	No data located		
Monoglycerides, hydrogenated tallow **61789-09-1**	No data located		
Glyceryl stearate **11099-07-3** and **67701-27-3**	No data located		
Glycerides, palm-oil mono-, hydrogenated **91744-73-9**	No data located		
Diglycerides			
Octadecanoic acid, 1,2-propanediol monoester **1323-39-3**	No data located		
Decanoic acid, ester with 1,2,3-propanetriol octanoate **65381-09-1**	*Danio rerio*/Similar to OECD 203/semi-static	>10,000 (nominal)	
Triglycerides			
Octanoin, tri- (Octanoic acid, 1,2,3-propanetriyl ester; Tricaprylin) **538-23-8**	No data located		
Hexanoic acid, 2-ethyl-, 1,2,3-propanetriyl ester **7360-38-5**	No data located		
Glycerides, C8-10 **85409-09-2**	No data located		
Glycerides, mixed decanoyl and octanoyl **73398-61-5**	*Danio rerio*/Directive 92/69/EEC, C.1/semi-static	>53 (measured)	
Oils, glyceridic, palm kernel **8023-79-8**	No data located		
Glycerides, C8-18 and C18-unsatd. **67701-28-4**	No data located		
Oils, vegetable, hydrogenated **68334-28-1**	No data located		
Glycerides, C12-18 **67701-26-2**	No data located		
Glycerides, C16-18 and C18-unsatd. **67701-30-8**	*Danio rerio*/Similar to OECD 203/semi-static daily renewal	>10,000 (nominal)	
Tallow, hydrogenated **8030-12-4**	No data located		
Castor oil, hydrogenated **8001-78-3**	*Danio rerio*/ ISO 7346/2/semi-static daily renewal	>10,000 (nominal)	

Olein, tri - (Octadecenoic acid, 1,2,3-propanetriyl) **122-32-7**	No data located		
Mixtures of mono-, di- and triglycerides			
Glycerides, C14-18 mono- and di- **67701-33-1**	*Danio rerio*/Similar to OECD 203/semi-static daily renewal	>10,000 (nominal)	
Glycerides, mixed coco, decanoyl and octanoyl **68606-18-8**	No data located		
Glycerides, C16-18 and C18-unsatd. mono- and di- **68424-61-3**	No data located		
Glycerides, C16-18 mono- and di- **85251-77-0**	No data located		
Glycerides, tall-oil mono-, di-, and tri- **97722-02-6**	*Danio rerio*/Similar to OECD 203/semi-static daily renewal	1700 (nominal)	
Glycerides, C16-18 and C18-unsatd. mono-, di- and tri- **91744-20-6**	No data located		
Coconut oil,transesterification products with decanoic acid mixed ester with glyceryl octanoate **68991-68-4** and **91052-53-8**	No data located		

Aquatic Invertebrates

Name and CAS Number	**Species/Test method**	**EC50 (mg/L) 48 hr**	
Monoglycerides			
Olein, mono- Octadecenoic acid, 1,2,3-propanetriol **25496-72-4**	No data located		
Glycerol oleate **37220-82-9**	No data located		
Glycerides,tall-oil **68309-32-0** and **61790-12-3**	*Daphnia magna*/OECD 202/static	EL50*>1000 (nominal)	
Octadecanoic acid, monoester with 1,2,3-propanetriol **31566-31-1**	No data located		
Monoglycerides, hydrogenated tallow **61789-09-1**	No data located		
Glyceryl stearate **11099-07-3** and **67701-27-3**	No data located		
Glycerides, palm-oil mono-, hydrogenated **91744-73-9**	No data located		
Diglycerides			
Octadecanoic acid, 1,2-propanediol monoester **1323-39-3**	No data located		
Decanoic acid, ester with 1,2,3-propanetriol octanoate **65381-09-1**	*Daphnia magna*/OECD 202/semi-static renewal every 2-3 days	EL50>100 (nominal; 21 d)	
Triglycerides			
Octanoin, tri- (Octanoic acid, 1,2,3-propanetriyl ester; Tricaprylin) **538-23-8**	No data located		
Hexanoic acid, 2-ethyl-, 1,2,3-propanetriyl ester **7360-38-5**	No data located		
Glycerides, C8-10 **85409-09-2**	No data located		
Glycerides, mixed decanoyl and octanoyl **73398-61-5**	*Daphnia magna*/EU Guideline 92/69/EWG/static	EL50>100 (nominal)	
	Daphnia magna/EU Guideline 92/69/EWG/static	EL50>100 (nominal)	
Oils, glyceridic, palm kernel **8023-79-8**	No data located		
Glycerides, C8-18 and C18-unsatd. **67701-28-4**	No data located		

Oils, vegetable, hydrogenated **68334-28-1**	No data located		
Glycerides, C12-18 **67701-26-2**	No data located		
Glycerides, C16-18 and C18-unsatd. **67701-30-8**	*Daphnia magna*/similar to OECD 202/semi-static renewal every 2-3 days	EL50>100 (nominal; 21 d)	
Tallow, hydrogenated **8030-12-4**	*Daphnia magna*/similar to OECD 202/static	EL50>100 (nominal)	
Castor oil, hydrogenated **8001-78-3**	No data located		
Olein, tri - (Octadecenoic acid, 1,2,3-propanetriyl) **122-32-7**	*Daphnia magna*/EU Guideline 92/69/EWG/static	EL50>100 (nominal)	
Mixtures of mono-, di- and triglycerides			
Glycerides, C14-18 mono- and di- **67701-33-1**	No data located		
Glycerides, mixed coco, decanoyl and octanoyl **68606-18-8**	No data located		
Glycerides, C16-18 and C18-unsatd. mono- and di- **68424-61-3**	No data located		
Glycerides, C16-18 mono- and di- **85251-77-0**	No data located		
Glycerides, tall-oil mono-, di-, and tri- **97722-02-6**	*Daphnia magna*/similar to OECD 202/static	EL50>100 (nominal)	
Glycerides, C16-18 and C18-unsatd. mono-, di- and tri- **91744-20-6**	No data located		
Coconut oil,transesterification products with decanoic acid mixed ester with glyceryl octanoate **68991-68-4** and **91052-53-8**	No data located		

Aquatic plants

Name and CAS Number	**Species/Test method**	**EC50 (mg/L), 72 hr**	
Monoglycerides			
Olein, mono- Octadecenoic acid, 1,2,3-propanetriol **25496-72-4**	No data located		
Glycerol oleate **37220-82-9**	No data located		
Glycerides,tall-oil **68309-32-0** and **61790-12-3**	*Pseudokirchnerella subcapitata*/ OECD 201/static	EbL50* = 854.9, ErL50 >1000 (nominal) NOELr = 500	
Octadecanoic acid, monoester with 1,2,3-propanetriol **31566-31-1**	No data located		
Monoglycerides, hydrogenated tallow **61789-09-1**	No data located		
Glyceryl stearate **11099-07-3** and **67701-27-3**	No data located		
Glycerides, palm-oil mono-, hydrogenated **91744-73-9**	No data located		
Diglycerides			
Octadecanoic acid, 1,2-propanediol monoester **1323-39-3**	No data located		
Decanoic acid, ester with 1,2,3-propanetriol octanoate **65381-09-1**	*Desmodesmus subspicatus*/ OECD 201/static	EbL50, ErL50 >100 (nominal), NOEL = 100	
Triglycerides			
Octanoin, tri- (Octanoic acid, 1,2,3-propanetriyl ester; Tricaprylin) **538-23-8**	No data located		

Hexanoic acid, 2-ethyl-, 1,2,3-propanetriyl ester **7360-38-5**	No data located		
Glycerides, C8-10 **85409-09-2**	No data located		
Glycerides, mixed decanoyl and octanoyl **73398-61-5**	*Desmodesmus subspicatus*/ OECD 201/static	EbL50, ErL50 >1000 (nominal loading), NOEC = 1000	
Oils, glyceridic, palm kernel **8023-79-8**	No data located		
Glycerides, C8-18 and C18-unsatd. **67701-28-4**	No data located		
Oils, vegetable, hydrogenated **68334-28-1**	No data located		
Glycerides, C12-18 **67701-26-2**	No data located		
Glycerides, C16-18 and C18-unsatd. **67701-30-8**	*Desmodesmus subspicatus*/ similar to OECD 201/static	EbL50, ErL50 >100 (nominal), NOEL =100	
Tallow, hydrogenated **8030-12-4**	*Desmodesmus subspicatus*/ similar to OECD 201/static	EbL50, ErL50 >100 (nominal), NOEL = 100	
Castor oil, hydrogenated **8001-78-3**	No data located		
Olein, tri - (Octadecenoic acid, 1,2,3-propanetriyl) **122-32-7**	No data located		
Mixtures of mono-, di- and triglycerides			
Glycerides, C14-18 mono- and di- **67701-33-1**	No data located		
Glycerides, mixed coco, decanoyl and octanoyl **68606-18-8**	No data located		
Glycerides, C16-18 and C18-unsatd. mono- and di- **68424-61-3**	No data located		
Glycerides, C16-18 mono- and di- **85251-77-0**	No data located		
Glycerides, tall-oil mono-, di-, and tri- **97722-02-6**	*Skeletonema costatum*/ ISO 10253 1995/static	ECr50 = 13.88 (nominal; exceeds the estimated water solubility of the substance)	
Glycerides, C16-18 and C18-unsatd. mono-, di- and tri- **91744-20-6**	No data located		
Coconut oil,transesterification products with decanoic acid mixed ester with glyceryl octanoate **68991-68-4** and **91052-53-8**	No data located		

*WAF sample preparations are reported relative to a loading rate rather than a concentration [LL50 (fish); EL50 (daphnia); EbL50/ErL50 (algae)]

There were no acute effects of the Glycerides Category members on fish, aquatic invertebrates or algae with LC50/LL50 or EC50/EL50 values less than the water solubility of the substance or that were less than 100 mg/L; similar results are expected for the Glycerides Category members that have not been tested.

There were no chronic reproductive effects of **CAS 65381-09-1** (diglyceride) or **67701-30-8** (triglyceride) on *Daphnia magna* (OECD 202), with NOEL (for reproduction) values > 100 mg/L; a concentration which exceeds the water solubility of the substances. Similar results are expected for the Glyceride Category members that have not been tested.

The Glycerides Category members do not possess properties indicating a hazard for the environment. Category members are rapidly biodegradable and have a low potential for bioaccumulation. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the

OECD Cooperative Chemicals Assessment Programme.

Exposure

The 2012 production volumes reported by the US EPA (Chemical Data Reporting (CDR)) for the sponsored Glycerides in the United States is as follows:

Name and CAS Number	Production volume (Tonnes/year)
Monoglycerides	
Olein, mono- Octadecenoic acid, 1,2,3-propanetriol **25496-72-4**	454 – 4,536
Glycerol oleate **37220-82-9**	454 – 4,536
Glycerides,tall-oil **68309-32-0** and **61790-12-3**	1,076
Octadecanoic acid, monoester with 1,2,3-propanetriol **31566-31-1**	454 – 4,536
Monoglycerides, hydrogenated tallow **61789-09-1**	28
Glyceryl stearate **11099-07-3** and **67701-27-3**	31 and 423
Glycerides, palm-oil mono-, hydrogenated **91744-73-9**	(b)
Diglycerides	
Octadecanoic acid, 1,2-propanediol monoester **1323-39-3**	(b)
Decanoic acid, ester with 1,2,3-propanetriol octanoate **65381-09-1**	(c)
Triglycerides	
Octanoin, tri- (Octanoic acid, 1,2,3-propanetriyl ester; Tricaprylin) **538-23-8**	(b)
Hexanoic acid, 2-ethyl-, 1,2,3-propanetriyl ester **7360-38-5**	35
Glycerides, C8-10 **85409-09-2**	(b)
Glycerides, mixed decanoyl and octanoyl **73398-61-5**	454 – 4,536
Oils, glyceridic, palm kernel **8023-79-8**	22,680 -45,359
Glycerides, C8-18 and C18-unsatd. **67701-28-4**	113,398 - 226,796
Oils, vegetable, hydrogenated **68334-28-1**	454 – 4,536
Glycerides, C12-18 **67701-26-2**	Not listed on CDR
Glycerides, C16-18 and C18-unsatd. **67701-30-8**	(c)
Tallow, hydrogenated **8030-12-4**	17
Castor oil, hydrogenated **8001-78-3**	5885
Olein, tri - (Octadecenoic acid, 1,2,3-propanetriyl) **122-32-7**	45-227
Mixtures of mono-, di- and triglycerides	
Glycerides, C14-18 mono- and di- **67701-33-1**	4,536 - 22,680
Glycerides, mixed coco, decanoyl and octanoyl **68606-18-8**	(b)
Glycerides, C16-18 and C18-unsatd. mono- and di- **68424-61-3**	454- 4536
Glycerides, C16-18 mono- and di- **85251-77-0**	(c)
Glycerides, tall-oil mono-, di-, and tri- **97722-02-6**	445
Glycerides, C16-18 and C18-unsatd. mono-, di- and tri- **91744-20-6**	(b)
Coconut oil,transesterification products with decanoic acid mixed ester with glyceryl octanoate **68991-68-4** and **91052-53-8**	(b)

(b) No production volumes reported to the EPA either because the substance is not produced in the US or substance or manufacturers are exempt from reporting.
(c) Production Information withheld in order to maintain Confidential Business Information (CBI)

In U.S., the main applications are in personal care products, cosmetics, cleaning products, industrial intermediates and in pharmaceuticals.

Glycerides are naturally occurring substances. Exposures to those used in industry could arise in association with production, formulation and industrial use of these substances.

Glycerides are manufactured in established chemical manufacturing facilities that have standard engineering controls and procedures in place to ensure safe handling and use of chemicals. The precautions used includes corrosion-resistant vessels and piping of the type used for any quality-controlled chemical reaction. Glycerides have a low volatility and as a rule engineering controls are available that prevent the need for respiratory protection. For routine operations, including those involving a breach of the closed system, goggles or safety glasses, gloves, safety boots and helmets are worn, and a higher level of respiratory protection is applied and extra measures may be taken to prevent breathing of vapours, if (local) ventilation is inadequate. Formulation of large volumes of product occurs in a continuous process using a closed system; for smaller volumes, a batch process is used. Closed reactors and/or mixing tanks with closed charging systems are typically used for the formulation of

glycerides.

Exposure to glycerides through the use of formulated products in industry and commerce is mitigated by following the recommended use and precaution instructions detailed in the material safety data sheet (MSDS). MSDS' reflect the hazard potential of the chemical ingredients in the product and provide details on the precautions necessary when handling these products and the instructions for first aid in case of an accidental exposure.

Major routes of consumer exposure to glycerides are from the use of glycerides in personal care products and cosmetics. Indirect consumer exposure to glycerides may occur from exposures to residual levels of down-the-drain products in receiving waters from effluents of sewage treatment plants.

Note: This document may only be reproduced integrally. The conclusions in this document are intended to be mutually supportive, and should be understood and interpreted together.

ORIGINAL SUBMISSION

LEWIS &
HARRISON
Consultants in Government Affairs

122 C Street, N.W., Suite 505
Washington, D.C. 20001
telephone 202.393.3903
fax 202.393.3906

November 20, 2012

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

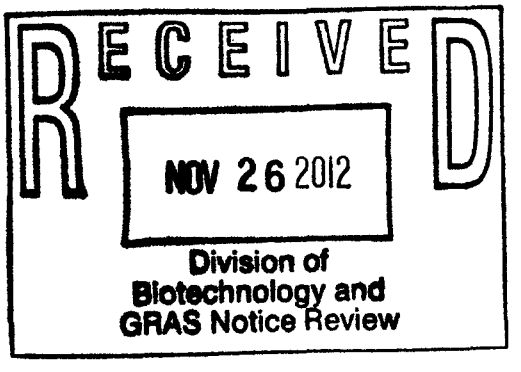
Re: Notification of the GRAS Determination of Medium Chain Triglycerides When Added Directly to Human Food

Dear Sir or Madam:

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

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

Please let me know if you have any questions.



Name and Address of Notifier

Lonza Inc.
attn: Robert Sloan
90 Boroline Road
Allendale, NJ 07401
Telephone: (201) 316-9365
Facsimile: (201) 696-3569
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90 Boroline Road
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122 C Street, NW, Suite 505
Washington, DC 20001
Telephone: 202-393-3903, ext. 14
Facsimile: 202-393-3906
e-mail: eharrison@lewisharrison.com

Names and Identity of GRAS Substance

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

Applicable Conditions of Use

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

- Food Types: Baked goods, beverages, chewing gum, confections and frostings, dairy product analogues, fats and oils, frozen dairy desserts, processed fruits, snack foods, adult nutritionals, cheeses and cheese spreads and soft candies.

- Functional Uses: Emulsifier, energy source, formulation aid, lubricant, release agent, nutrient supplement, processing aid, solvent, vehicle, stabilizer, thickener, surface finishing agent, and texturizer.

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

Basis for GRAS Determination

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

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

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

Detailed Information Concerning the Identity of the Notified Substance

A. Identity

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

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

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

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

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

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

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

B. Composition

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

MCTs are a unique class of lipids composed mainly of caprylic (C_8; 50-80%) and capric fatty acids (C_{10}; 20-50%) with a minor level of caproic (C_6; 1-2%) and lauric (C_{12}; 1-2%) fatty acids. They are derived from common edible oils rich in free medium chain fatty acids such as coconut or palm oil. Compositional analysis indicates that the fatty acids present are the type commonly found in other edible oils.

C. Method of Manufacture of Medium Chain Triglycerides

Edible Vegetable Oil
↓
Fractionation
↓
Lipase Esterification
↓
MCT crude

Filtration to remove lipase
↓
MCT Lipase-free

Deacidification
↓
Bleaching, deodorizing
↓
Packing, Quality analysis
↓
Finished MCT Product

D. Specifications for Food Grade MCT

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

E. Self Limiting Levels of Use

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

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

F. GRAS Exemption Claim

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

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

Availability of Information:

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

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

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

Sincerely yours,

Eliot Harrison
Lewis & Harrison LLC
Agent for Lonza Inc.

SUBJECT:

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

NOTIFER:

Lonza Inc.
Allendale, N.J.

DATE:

November 20, 2012

Table of Contents

1. GRAS EXEMPTION CLAIM

Lonza Inc. is filing this GRAS Notification to:

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

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

(i) Notifier

Lonza Inc.
attn: Robert Sloan
90 Boroline Road
Allendale, NJ 07401
Telephone: (201) 316-9365
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Lewis & Harrison, LLC
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122 C Street, NW, Suite 505
Washington, DC 20001
Telephone: 202-393-3903, ext. 14
Facsimile: 202-393-3906
e-mail: eharrison@lewisharrison.com

(ii) Name of GRAS Substance

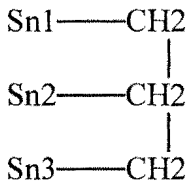
Medium Chain Triglycerides (MCTs), CAS No. 73398-61-5

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

MCTs are a unique class of lipids that are composed mainly of caprylic (C_8; 50-80%) and capric fatty acids (C_{10}; 20-50%) with a minor level of caproic (C_6; 1-2%) and lauric (C_{12}; 1-2%) fatty acids. They are derived from common edible oils rich in free medium chain fatty acids, such as coconut or palm oil. Compositional analysis indicates that the fatty acids present are the type commonly found in other edible oils.

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

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



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

(iii) Conditions of Use

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

- Food Types: Baked goods, beverages, chewing gum, confections and frostings, dairy product analogues, fats and oils, frozen dairy desserts, processed fruits, snack foods, adult nutritionals, cheeses and cheese spreads and soft candies.

- Functional Uses: Emulsifier, energy source, formulation aid, lubricant, release agent, nutrient supplement, processing aid, solvent, vehicle, stabilizer, thickener, surface finishing agent, and texturizer.

(iv) Basis for GRAS Determination

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

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

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

2. Description, Manufacturing Process and Specifications

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

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

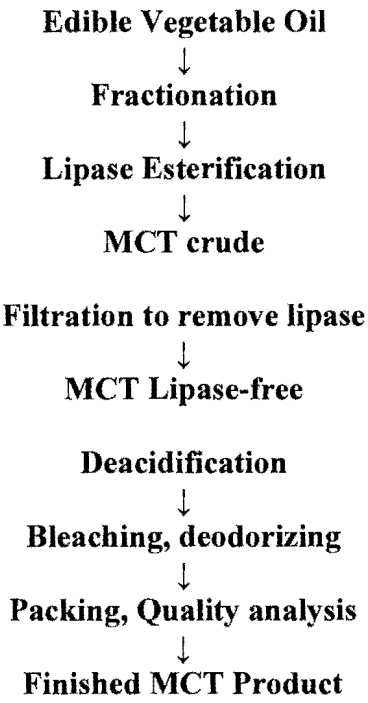


Figure 2. Medium Chain Triglyceride Production Scheme

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

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

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

(ii). Specifications for MCT

Product Information, Lonza Group

The product is MCT- Medium Chain Triglycerides.
Kosher Food Grade
Fractionated Coconut Oil Ester
CAS No. 73398-61-5
INCI Designation: Caprylic/Capric Triglyceride

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

Typical Properties	
Appearance	Clear liquid
Odor	Neutral
Taste	Neutral

3. Dietary Intake

Recent subchronic studies in humans have provided confirmation of earlier dietary studies and show that MCTs exhibit very low toxicity when administered in the diet at levels up to 15% of the diet. MCT-based diets have been shown to cause minor alterations in serum lipid profiles, which have occasionally translated into slower rates of weight gain relative to long-chain triglyceride-based diets (Traul, *et al.*, 2000).
Many studies in humans that will be discussed in detail in this notification estimate that MCTs have typically been used in diets for children at 15-30 gm/day, and 40-100 gm/day in adults, covering up to 40% of the daily energy requirements (Bach, *et al.*, 1996).
Studies of MCTs carried out recently (Chanez, 1991; Webb, 1993) are consistent with regard to the observations that MCTs can be administered by various routes at relatively high dose levels, especially in the diet or by oral gavage, without significant adverse effects. NOAEL values from dietary studies appear to be consistently of the order of

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

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

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

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

Upon ingestion, MCTs are partially hydrolyzed to medium chain fatty acids (MCFAs) by buccal, lingual, gastric, intestinal, and pancreatic lipases in the stomach, and then completely broken down by pancreatic lipase inside the intestinal lumen to form free fatty acids and glycerol. MCFAs are more hydrophilic than long chain fatty acids (LCFAs), the majority of MCFA do not require micelle-containing bile salts or chylomicron formation, but are directly absorbed into the liver via the portal vein rather than through the thoracic duct lymph system that is the conventional route for the absorption of triglycerides containing long-chain fatty acids. A minor fraction of MCFAs bypass the liver and are distributed to peripheral tissues via the general circulation (Babayan, 1988; Bach and Babayan, 1982; Traul, *et al.*, 2000). The MCFAs are catabolized predominantly in the liver to C_2 fragments such as acyl CoA esters. The C_2 fragments are further converted to CO_2, or used to synthesize longer-chain fatty acids. Very little of the MCT, if any, is stored in adipose tissues (Greenberger and Skillman, 1969; Traul *et al.*, 2000). Medium chain fatty acyl CoAs (mainly of caprylic and capric acids), in the hepatocytes, are transported across the mitochondrial membrane via a carnitine-independent mechanism. Once in the mitochondria, they are metabolized, initially by medium-chain acyl CoA dehydrogenase, to acetoacetate and betahydroxybutyrate (Schwab *et al.*, 1964; Babayan, 1987; Bell *et al.*, 1997). Acetoacetate and betahydroxybutyrate may be further metabolized in the liver to CO_2, water and energy, and may enter other metabolic pathways in the liver or be transported by the systemic circulation to other tissues, where they are metabolized to produce CO_2,

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

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

The hepatic mitochondrial metabolism of MCFAs such as caprylic and capric acid ultimately results in an excess of acetyl-CoA that in turn results in the production of acetate, CO_2 and ketone bodies, with a minor portion serving to lengthen endogenous fatty acids (Bach and Babayan, 1982). However, some investigators have suggested that MCT diets, when fed in excess of caloric needs, might lead to increased *de novo* fatty acid synthesis and enhanced fatty acid elongation activity in the liver (Hill *et al.*, 1990). Most of the MCFAs are catabolized within the liver with only a minor portion reaching the general circulation bound to albumin.

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

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

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

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

5. Safety Evaluation

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

(i) Acute Studies

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

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

Another mouse study tested Miglyol 810 (slightly higher portion of C_8 fatty acids than Miglyol 812) at 12.5, 20.0 and 25.0 ml/kg. Transient ataxia, lethargy, dispnea and diuresis occurred within 15 minutes in the mid- and high-dose groups, and complete loss of activity was observed within 2 hours, followed by recovery, in several animals in the high dose. Deaths occurred within 24 to 48 hours in two animals that received 20 ml/kg and one animal that received 25 ml/kg. All symptoms disappeared in the survivors by the end of day 3. No necropsy observations were reported (Poole, 1977; Traul, *et al.*, 2000).

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

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

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

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

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

The acute toxicity of several mixed preparations of caprylic/capric acid triglyceride has also been investigated in a series of oral studies in mice and rats (Elder, 1980). This series of studies indicated that the oral LD50 for female mice was greater than 25 ml/kg. In the first mouse study, at a dose of 25 ml/kg, lethargy and ataxia were observed within 10 minutes of administration, and dyspnea within 1 hour. 24 hours after administration, all animals appeared asymptomatic and survival was 100%. In the second mouse study, using dose ranges from 12.5 to 25 ml/kg, ataxia, lethargy and dyspnea were noted within 15 minutes, which progressed to a complete loss of activity in a few animals by 1 hour. At doses of 20 and 25 ml/kg, three deaths out of 15 animals occurred within 48 hours (20% mortality); surviving animals were asymptomatic by 72 hours (Traul, *et al*, 2000).

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

(ii) <u>Subchronic Toxicity Studies</u>

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

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

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

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

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

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

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

In a 6-week study, no significant adverse effects were observed when 15 male Sprague-Dawley rats were fed, via oral intubation, either an MCT- or an LCT-containing diet that derived 50% of the calories from fat. Animals fed the MCT diet had significantly lower levels of dissectable fat, which was attributed to higher resting and maximal norepinephrine-stimulated O_2 consumption and metabolic rate. Liver fat and blood glucose values were comparable between the two groups (Baba, *et al.*, 1982).

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

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

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

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

(iii) Reproduction and Developmental Studies

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

(iv) Chronic Toxicity/Carcinogenicity Studies

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

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

The National Toxicology Program (NTP) tested tricaprylin, a triglyceride in which all three fatty acids are C_8, (caprylic acid) in a 2-year chronic toxicity and carcinogenicity study. In this study, male F344/N rats were gavaged with 0, 2.5, 5 or 10 ml tricaprylin/kg body weight daily, 5 days/week for 2 years.

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

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

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

(v) Genotoxicity Studies

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

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

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

(vi) Clinical Studies

Human clinical studies have also been reported using MCTs as a fat source. A study was conducted with eight patients who were fed formula diets containing either MCTs (77.7% C_8 (caprylic), 19.6% C_{10} (capric), 1.9% C6 and 0.8% C_{12}), butter or corn oil as sole isocaloric source of dietary fat. The study lasted up to 10 weeks and used a crossover study design; each formula derived 40% of its caloric content from fat. The MCT- and corn oil-containing diets were shown to produce significantly lower cholesterol levels, relative to steady-state levels achieved on the butter diet. The only side effect documented for the MCT formula was a transient period of nausea and abdominal fullness during the first 3-4 days (Hashim, et al., 1960; Traul, et al., 2000).

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

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

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

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

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

(vii) Sensitive Populations

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

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

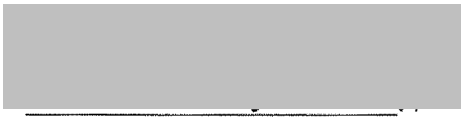
It also appears highly unlikely that the consumption of MCTs in the diet would pose any concern for neurological effects as a result of the metabolic release of caprylic acid (Traul, *et al.*, 2000).

6. Conclusion

Due to its unique absorption and metabolism characteristics, MCT oil has been used therapeutically since the 1950s. MCTs have also been used in an increasing number of food and nutrition applications as they offer a number of advantages over long-chain triglycerides, which are metabolized differently and absorbed less quickly. MCTs have been evaluated in acute, subchronic, reproductive, developmental chronic/carcinogenicity and genotoxicity studies in mammals, and in a number of human clinical studies. The data strongly suggest that MCTs would pose little or no risk from toxicity when consumed as a supplement in a balanced diet at levels up to 15% of the dietary calories or about 50% of the dietary fat.

7: Certification

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



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SUBMISSION END

Amended Safety Assessment of Triglycerides as Used in Cosmetics

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ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of 51 triglycerides; 25 of these ingredients were previously reviewed by the Panel, and 26 are reviewed herein for the first time. The majority of the ingredients named in this assessment have several functions, with most reported to function as skin conditioning agents (occlusive or emollient) and/or viscosity increasing agents in cosmetics; some are also reported to function as a fragrance or solvent. The Panel reviewed relevant new data, including frequency and concentration of use, and considered the data from previous CIR reports. The Panel concluded the 51 triglycerides reviewed in this report are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

The Panel published the Final Report on the Safety Assessment of Trihydroxystearin in 2000.[1] Based on the available animal and clinical data, which included summary data from the CIR safety assessments of Hydroxystearic Acid and Glyceryl Stearate and Glyceryl Stearate SE, the Panel concluded that Trihydroxystearin is safe as used in cosmetics. In 2015, the Panel re-evaluated the safety of Hydroxystearic Acid and Glyceryl Stearate and Glyceryl Stearate SE, reaffirming that Hydroxystearic Acid is safe as a cosmetic ingredient in the present practices of use and concluding that Glyceryl Stearate and Glyceryl Stearate SE are safe in the present practices of use and concentration.[2] (In 1982, the conclusion issued for Glyceryl Stearate and Glyceryl Stearate SE was safe for topical application to humans.[3])

The Panel issued two additional reports on related ingredients. In 2001, the Final Report on the Safety Assessment of Trilaurin and 22 additional glyceryl triesters was published,[4] and in 1980, the Final Report of the Safety Assessment for Caprylic/Capric Triglyceride was published.[5] In both safety assessments, the Panel reached the conclusion that the ingredients are safe as used in cosmetics. (In 2003, the Panel reaffirmed that conclusion for Caprylic/Capric Triglyceride.[6]) The 25 ingredients reviewed in the three reports are now included in this re-review:

Caprylic/Capric Triglyceride
Glyceryl Stearate Diacetate
Glyceryl Triacetyl Hydroxystearate
Glyceryl Triacetyl Ricinoleate
Triarachidin
Tribehenin
Tricaprin
Tricaprylin
Trierucin
Triheptanoin
Triheptylundecanoin
Trihydroxystearin
Triisononanoin
Triisopalmitin
Triisostearin
Trilaurin
Trilinolein
Trimyristin
Trioctanoin (now, Triethylhexanoin)
Triolein
Tripalmitin
Tripalmitolein
Triricinolein
Tristearin
Triundecanoin

In accordance with its procedures, the CIR evaluates the conclusions of previously-issued reports every 15 years, and it has been at least 15 years since these assessments have been issued. Because each report was reviewed 15+ years ago and they all comprise triglycerides, i.e., fatty acid triesters of glycerin, and because the collection of these ingredients in one report enables the assembly of reinforcing and complementary test data, the Panel determined these reports should be re-reviewed together in one document; this family is referred to as the triglycerides.

Also included in this assessment are 26 triglycerides named in the web-based *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*) that have not been reviewed:

Acetic/Linoleic/Palmitic Triglyceride
C8-12 Acid Triglyceride
C12-18 Acid Triglyceride
C18-36 Acid Triglyceride
Capric/Lauric/Myristic/Oleic Triglyceride
Caprylic/Capric/Lauric Triglyceride
Caprylic/Capric/Linoleic Triglyceride
Caprylic/Capric/Myristic/Stearic Triglyceride
Caprylic/Capric/Palmitic/Stearic Triglyceride
Caprylic/Capric/Stearic Triglyceride
C10-40 Isoalkyl Acid Triglyceride
Cod Liver/Mink/Tallow Triglyceride
C10-18 Triglycerides
Docosahexenoic/Docosapentenoic/Oleic/Palmitic Triglyceride
Glyceryl Tri-Hydrogenated Rosinate
Glyceryl Tripalmate/Palm Kernelate/Olivate/Macadamiate/Rapeseedate
Hydrogenated C12-18 Triglycerides
Isomerized Safflower Glycerides
Jojoba Oil/Caprylic/Capric Triglyceride Esters
Lauric/Palmitic/Oleic Triglyceride
Oleic/Linoleic Triglyceride
Oleic/Palmitic/Lauric/Myristic/Linoleic Triglyceride
Palmitic/Stearic Triglyceride
Ricinoleic/Caproic/Caprylic/Capric Triglyceride
Trilinolenin
Tripelargonin

A consolidated list of the 51 ingredients included in this review is provided in Table 1.

According to the *Dictionary*, the majority of the ingredients named in this assessment have several functions, with most reported to function as skin conditioning agents (occlusive or emollient) and/or viscosity increasing agents in cosmetics; some are also reported to function as a fragrance or solvent.[7] An exception is Glyceryl Tri-Hydrogenated Rosinate, which is only reported to function as a surfactant – emulsifying agent. A reported function of Docosahexenoic/Docosapentenoic/

Oleic/Palmitic Triglyceride is skin bleaching agent; skin bleaching agent is not a cosmetic function, and therefore use in that manner is not being assessed in this report. A complete listing of all the functions for each ingredient is given in Table 2.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that CIR typically evaluates, is provided on the CIR website (http://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; http://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Excerpts from the summaries of the reports on the previously reviewed ingredients (as provided in those reports) are disseminated throughout the text of this re-review document, as appropriate, and are identified by *italicized text*. (This information is not included in the tables or the summary section.) For complete and detailed information, please refer to the original documents, which are available on the CIR website (http://www.cir-safety.org/ingredients). Additionally, the Discussions from the Trihydroxystearin (2000) and Trilaurin (2001) assessments are also included in this document.

The triglycerides all share a glycerin core. The Panel evaluated the safety of glycerin as used in cosmetics in 2014, concluding that glycerin is safe in cosmetics in the present practices of use and concentration described in the safety assessment.[8] Additionally, the Panel reviewed the safety of 44 monoglyceryl monoesters in 2015, concluding that those ingredients are safe in the present practices of use and concentration,[2] and of a group of diglycerides in 2007, concluding this family of ingredients is safe in the present practices of use and concentration provided the content of 1,2-diesters is not high enough to induce epidermal hyperplasia.[9] Many of the acid components and related glyceryl esters of these triglycerides have also been reviewed by CIR. A listing of those that have been reviewed, and the associated conclusions, is provided in Table 3.

Finally, much of the new data included in this safety assessment was found on the European Chemicals Agency (ECHA) website.[10] Please note that the ECHA website provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited.

CHEMISTRY

Definition and Structure

The definitions and structures of the ingredients included in this triglyceride group are provided in Table 2 and are presented in order of increasing chain length, subdivided by chain type. (Toxicity data are presented in the same order.).

Each of the ingredients in this report is a triglyceride; triglycerides are the fatty acid triesters of glycerin. Subsequently, each of the ingredient structures in this report contains a glycerin core, tri-substituted with fatty acid residues.

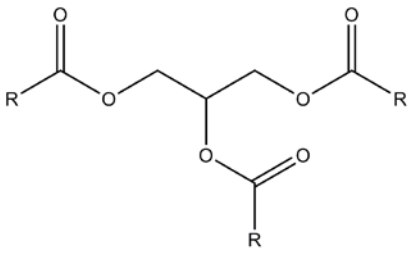


Figure 1. Triglycerides, wherein each "RC(O)-" is a fatty acid residue

For example, Tricaprylin is the triester of caprylic acid with glycerin.

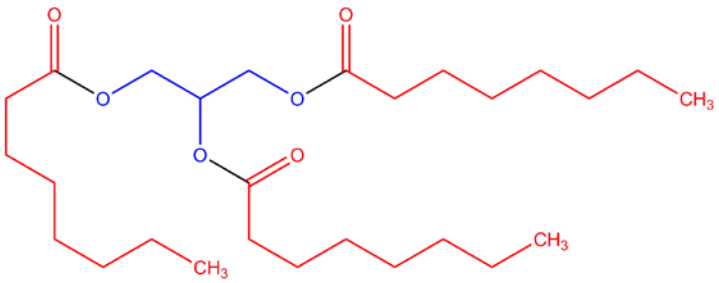


Figure 2. Tricaprylin (the triester of caprylic acid with glycerin)

Physical and Chemical Properties

Triglycerides are hydrophobic materials that range from oils, at the lowest molecular weights/shortest chain-lengths, to waxy solids, at the highest molecular weights/longest chain-lengths. Physical and chemical properties are presented in Table 4.

Methods of Manufacture

One method of production of Trihydroxystearin involves the hydrogenation of castor oil, in the presence of the reagent nickel, at a temperature of 200ºC. Another method of production is the reduction of triricinolein.[1]

Trilaurin may be produced by reacting glycerin with lauric acid or glycerin with lauroyl chloride (reagent: pyridine or quinoline).[4] *The reaction of lauric acid with glycerin is another method of production. Triolein may be prepared by the esterification of oleic acid. Tripalmitin can be prepared from glycerin and palmitic acid in the presence of either Twitchell reagent or trifluoroacetic anhydride. Tristearin may be prepared from stearic acid and glycerin in the presence of* Al_2O_3*. Triundecanoin is produced by esterification of undecanoic acid and glycerin. The undecanoic acid is produced from castor oil, which is hydrolyzed to fatty acids and subjected to thermal degradation and fractionation. The resulting undecenoic acid is transformed to undecanoic acid and reesterified to the glycerin moiety. Deodorization, the final step, is accomplished using steam to remove components that give rise to unwanted flavors and odors.*

Caprylic/Capric Triglyceride is manufactured by hydrolyzing coconut oil, removing the free glycerin, and separating the medium chain length fatty acids by fractional distillation.[5] *The acids are then blended in the proper ratio and re-esterified with glycerin.*

Triglycerides (general)

Some of the triglycerides are produced synthetically via classical Fischer type esterification methods (i.e., reaction of carboxylic acids with glycerin to produce carboxylic esters), although the reaction may be promoted by acid or base catalysis, or by the use of an acid chloride. However, some of these ingredients may be natural sourced and produced by transesterification (i.e., exchange of acid moieties to create a different ester product). For example, the triglycerides in natural oils can be reacted with intended length fatty acids to produce new triglycerides.

The following are method of manufacture schemes for Caprylic/Capric Triglyceride (medium-chain triglycerides (MCT); terminology used in a FDA foods Generally Recognized as Safe (GRAS) notification, defined as triglycerides with alkyl chain lengths from 8 to 10 carbons long) (Figure 3)[11] and medium- and long-chain triacylglycerol (MLCT)-oil (terminology used in a FDA foods GRAS notification, defined as triglycerides with alkyl chain lengths from 8 to 24 carbons long) (Figure 4):[12]

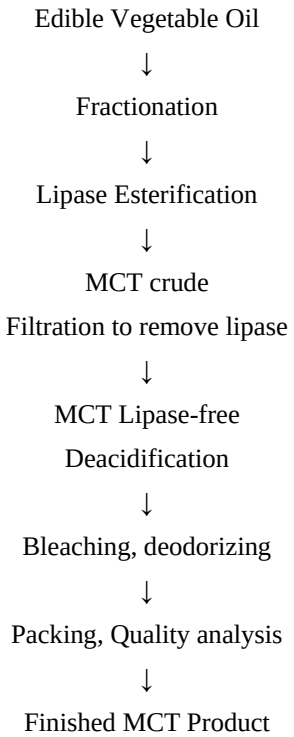


Figure 3. Caprylic/Capric Triglyceride (MCT) production scheme

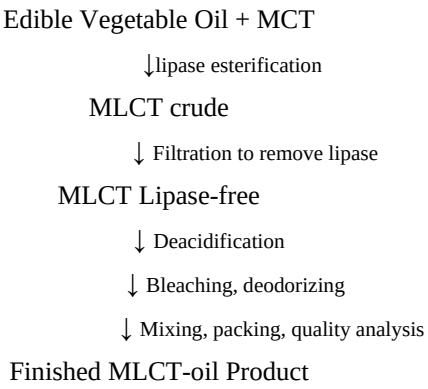


Figure 4. MLCT production scheme

Impurities

Triundecanoin contains no impurities or residues of catalysts or solvents.[4] *1,4-Dioxane, ethylene oxide, free amines, and nitrosamines are not added or formed during the production process. Furthermore, volatile compounds are effectively removed, by the deodorization process, below detection limits (0.1 ppm). The deodorization process also has removed any organochlorine or organophosphorus pesticides that may be present in the crude oil used in the production process. It is also important to note that the total content of polycyclic aromatic hydrocarbons (PAHs), if present in the crude oil, is reduced below 10 ppb. Additionally, aflatoxins, if present in the raw materials, are reduced below detection limits (0.5 ppb) by neutralization and bleaching.*

The only known impurities of Caprylic/Capric Triglyceride are approximately 300 ppm free fatty acids and as much as 0.2% glycerin.[5] *The relatively low iodine number 5, which is determined in an arbitrary but standard method, indicates very little unsaturated material present.*

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this safety assessment is evaluated based on data received from the FDA and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA VCRP database. Use concentration data are submitted by the cosmetic industry in response to a survey, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to information from the VCRP and that received from the Council, 30 ingredients assessed in this report are in use. Caprylic/Capric Triglyceride has the highest frequency of use; according to 2017 VCRP data, it is used in 6000 cosmetic formulations, with uses reported for all exposure types.[13] Tribehenin has the next highest frequency of use, with 723 reported uses, followed by Triethylhexanoin, with 601 reported uses. (Table 5; Table 6)

Use concentration survey data were collected in 2015/2016 (and updated in 2017) for some of ingredients,[14] and in 2017 for the remaining ingredients.[15] The results indicate that Triethylhexanoin has the highest maximum use concentration in leave-on formulations, with concentrations of 100% reported for face and neck formulations and 63% in lipstick formulations (Table 5). Caprylic/Capric Triglyceride has the next highest maximum use concentration in leave-ons, with concentrations of 95.6% in face and neck products.

Approximately half of the ingredients included in this safety assessment have been reviewed previously by the Panel. The frequency and maximum concentrations of use for the majority of these ingredients has increased when compared to the previous review. The most remarkable increase is in the frequency of use of Caprylic/Capric Triglyceride; in 2003, this ingredient was reported to be used in 763 formulations and in 2017, it is reported to be used in 6000 formulations.[5,6] Concentrations of use have also increased.[6,14] In 2003, the maximum leave-on concentration of use for this ingredients was 84%, it is now reported to 95.6%; maximum concentrations of use increased for eye area, non-coloring hair, hair coloring, nail, and baby product formulations. The increase in baby products was quite notable, increasing from 0.8% to 52%.

The 21 triglycerides not currently reported to be in use, according to VCRP and concentration of use survey data, are listed in Table 7.

In some cases, reports of use were received from the VCRP, but no concentration of use data were provided. For example, Trilinolenin is reported to be used in 2 formulations,[16] but no use concentration data were provided. In other cases, no uses were reported to the VCRP, but a maximum use concentration was provided in the industry survey. For example,

Caprylic/Capric/Linoleic Triglyceride was not reported in the VCRP database to be in use, but the industry survey indicated that it is used at concentrations up to 52.1% in body and hand product formulations.[15] It should be presumed that Caprylic/ Capric/Linoleic Triglyceride is used in at least one cosmetic formulation for each category for which it is reported to be used.

Some of the triglycerides are used at relatively high concentrations in products that can be used near the eye, can possibly be ingested, or come in contact with mucous membranes; for example, Caprylic/Capric Triglyceride is used at up to 83.3% in eye lotions, and Triethylhexanoin is used at up to 63% in lipstick formulations. Additionally, some of these ingredients are used in cosmetic sprays and powders and could possibly be inhaled; for example, Caprylic/Capric Triglyceride and Triethylhexanoin are reported to be used at maximum concentrations of 38% in spray body and hand formulations and 36% in perfumes, respectively, and 16% and 14.7%, respectively, in face powders. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm, with propellant sprays yielding a greater fraction of droplets/particles <10 µm compared with pump sprays.[17,18] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[19,20] Conservative estimates of inhalation exposures to respirable particles during the use of loose-powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[21-23] Caprylic/Capric Triglyceride is used at up to 0.99% in spray deodorant formulations. There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[20] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.

All the triglycerides described in this safety assessment (and listed in the *Dictionary*) are not restricted from use in any way under the rules governing cosmetic products in the European Union (EU).[24] In Australia, Triethylhexanoin cannot be classified as hazardous under the *Approved Criteria for Classifying Hazardous Substances*.[25]

Non-Cosmetic

Trihydroxystearin has been used as a thickening agent for peanut butter.[1] *FDA has listed the following indirect food additive uses in the Code of Federal Regulations (CFR): components of adhesives (21CFR 175.1 05), components of resinous and polymeric coatings (21 CFR 175.300), components of paper and paperboard in contact with aqueous and fatty foods (21 CFR 176.170), components of paper and paperboard in contact with dry food (21 CFR 176.180), defoaming agents used in the manufacture of paper and paperboard (21 CFR 176.21 0), cellophane (21CFR 177.1200), closures with sealing gaskets for food containers (21 CFR 177.1210), polyester resins cross-linked (21 CFR177.2420), and textiles and textile fibers (21 CFR 177.2800).*

Trihydroxystearin is among the inert ingredients that are exempt from the requirement of a tolerance under the Federal Food, Drug, and Cosmetic Act when used in pesticide formulations that are applied to crops.[1]

Trilaurin has been detected in pharmaceutical excipients.[4] *Tricaprylin has been used as an energy source for burn patients and for patients having difficulty digesting long-chain fatty acids. Tristearin has been approved for use as a direct food additive (21 CFR 172.811). Additionally, the following glyceryl triesters have been approved for use as components of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food (i.e., use as indirect food additives): Trilaurin, Trimyristin, Triolein, Tripalmitin, Tristearin (21 CFR 177.2800), and Glyceryl Triacetyl Hydroxystearate (21 CFR 178.3505).*

The following non-cosmetic uses of Tristearin have been reported: soap, candles, candies, adhesive pastes, metal polishes, waterproofing paper, textile sizing, leather stuffing, and manufacture of stearic acid.[4]

Letters issued by the FDA have attested to the safety of Caprylic/Capric Triglyceride when used as a food additive.[5] *In addition, it has also been marketed for consumption since 1962 as a nutritional supplement and blood lipid lowering agent. It has also been suggested for use in enteric drugs and rectal suppositories and as a vehicle for topically applied pharmaceuticals.*

C10-18 Triglycerides is approved for use as direct multipurpose food additives (21CFR172.861).

Caprylic/Capric Triglyceride and Triglycerides (general)

The FDA received a GRAS notification request for triglycerides (C8-C24) for use as a food ingredient, such that the total daily consumption would not exceed 31 g/day.[12] The FDA responded that the tailored triglycerides ingredient (12% Caprylic/Capric Triglyceride) is GRAS under the intended conditions of use as an oil in home cooking, salad dressings, vegetable-oil spreads, and frozen dinners (including meat and poultry).[26] The agency has not, however, made its own determination regarding the GRAS status of the subject use of the tailored triglycerides (12% Caprylic/Capric Triglyceride) ingredient.

Caprylic/Capric Triglyceride, is a component of a homogenous lipid emulsion approved for intravenous (i.v.) infusions indicated for use in adults as a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.[27] The lipid content of the infusion is 0.20 g/ml, and comprises a

mixture of soybean oil, Caprylic/Capric Triglyceride, olive oil, and fish oil; recommended dosing is 1 to 2 g/kg/day, not exceeding 2.5 g/kg/day.

TOXICOKINETIC STUDIES

Dermal Penetration

In mice and guinea pigs, little skin penetration was observed.[4] In the mice, ^{14}C-Triolein (undiluted or in hydrophilic ointment) did not penetrate into the body organs of mice, and the oil remained localized at the application site at 48 h post application.

Penetration Enhancement

Tricaprylin enhanced the skin penetration of drugs in vivo (Wistar rats) and in vitro (hairless mice).[4] The skin penetration enhancement of drugs in the presence of Triolein has been reported.

Absorption, Distribution, Metabolism, and Excretion

Metabolism data indicate that most triglycerides (or glyceryl triesters) are split into monoglycerides, free fatty acids, and glycerin in the small intestine and absorbed by the intestinal mucosa [4]

When absorbed from the digestive tract, Caprylic/Capric Triglyceride is hydrolyzed, and the fatty acids are catabolized to C_2 fragments which may be further metabolized either to CO_2 or to form long-chain fatty acids. [5] *Caprylic/Capric Triglyceride can undergo hydrolysis by enzymatic or chemical means to produce free fatty acids, partial glycerides, and glycerin. The free fatty acids may, in turn, undergo enzymatic β-oxidation. β-Oxidation of caprylic acid forms β-ketocaprylic acid and can be further oxidized to yield acetic acid and C_6,-acid*.

Caprylic/Capric Triglyceride and Triglycerides (general)

Oral absorption and metabolism of foods containing long-chain triglycerides (LCT) mixtures (alkyl chain lengths greater than 12 (C > 12)) differ from those containing Caprylic/Capric Triglyceride.[28] C > 12 are degraded by salivary, intestinal and pancreatic lipases into two fatty acids and a monoacyl glycerol, whereas, Caprylic/Capric Triglyceride is degraded by the same enzymes into three fatty acids and the simple glycerol backbone. Caprylic/Capric Triglyceride is readily absorbed from the small intestine directly into the bloodstream and transported to the liver for hepatic metabolism, while C > 12 are incorporated into chylomicrons and enter the lymphatic system. Caprylic/Capric Triglyceride is readily broken down to carbon dioxide and two-carbon fragments, while C > 12 are re-esterified to triacylglycerols and either metabolized for energy or stored in adipose tissue.

Tripelargonin and Triethylhexanoin

The primary metabolite of Triethylhexanoin, along with glycerol and monoglycerides, is 2-ethylhexanoic acid.[25]

Groups of 5 newborn Rhesus (*Macaca mulatta*) monkeys were administered 8.4 ml/kg bw Tripelargonin, Triethylhexanoin, or water (control) via nasogastric (NG) tube.[29] Plasma C8:0 and C9:0 fatty acids and whole blood D-(-)-3-hydroxybutyrate (3HB) levels were measured 0, 1, and 3 h after dosing. Free fatty acid concentrations and ketone 3HB increased with time. C8 and C9 levels did not differ at 1 or 3 h, but at 1 h, blood 3HB concentrations were higher with Triethylhexanoin compared to animals dosed with Tripelargonin.

Groups of 8 New Zealand male rabbits were given a Tripelargonin/LCT (7/3 wt/wt) emulsion via a total parenteral nutrition (TPN) infusion regimen 7 h/day for 11 days.[30] The 3HB concentrations were significantly decreased, and plasma concentrations of propionic, acetic, butyric, and valeric acids were significantly increased. Following overnight fasting on days 9 and 12, fatty glycerol concentrations were statistically significantly increased compared to controls that were fed a standard diet, and on day 12, fasted rabbits were found to have increased triglyceride and non-esterified fatty acid levels.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

In acute oral toxicity studies in which Trihydroxystearin was tested using albino rats, the LD_{50} was not achieved at a dose of 5 g/kg and no deaths were reported. [1]

Acute oral LD_{50} values range from 5 g/kg in mice (Tribehenin) to > 20 g/kg in rats (Tristearin).[4] In other acute oral toxicity studies, Triethylhexanoin [Trioctanoin] was not toxic following oral administration to male mice at a dose of 50 ml/kg, and Triisostearin did not induce toxicity in rats at a dose of 2 g/kg.

Acute oral LD_{50} values for Caprylic/Capric Triglyceride were > 25 ml/kg in mice and >5 g/kg in rats.[5] *Male rats and guinea pigs in groups of ten each were exposed for 6 h in a 40 L chamber containing an aerosol of Caprylic/Capric Triglyceride at a nominal concentration of 28.1 µl/l of air. The fraction of the aerosol with particles small enough to be inhaled into the lung, i.e., with a diameter of 5 µm or less, represented 1.97 µl/l of the test substance. No adverse effects were observed.*

The acute dermal and oral toxicity studies summarized below are described in Table 8.

The dermal LD_{50} in rats was >2 g/kg (the highest dose tested) for both Triheptanoin[31] and Tristearin.[32] The oral LD_{50} was >2 g/kg for Triisostearin in mice and rats,[33] >2 g/kg Triolein in mice,[34] >5 g/kg Triheptanoin in mice, and >48 g/kg Triethylhexanoin[35] in rats. The oral LD_{50} of an MLCT oil was >5 g/kg in rats.[28] A single dose of 8.4 ml/kg bw Tripelargonin and Triethylhexanoin, administered via NG tube, did not affect activity level or induce narcolepsy in newborn Rhesus (*Macaca mulatta*) monkeys.[29]

Short-Term Toxicity Studies

The short-term oral administration of Trilaurin, Tristearin, or Triolein to weanling rats did not result in gross or microscopic lesions.[4] *However, in another short-term study, significant differences in hematological and clinical chemistry parameters as well as organ weights were noted after administration of Tricaprylin to male and female Wistar rats.*

No signs of toxicity were observed in rabbits following 4 wks of applications of a tanning butter formulation containing 22% Caprylic/Capric Triglyceride at a dose of 2 g/kg, five times/wk for 4 wks, to intact and abraded skin.[5] *Two groups of 10 rats were dosed by gavage with 7.6 or 21.3 ml/kg undiluted Caprylic/Capric Triglyceride daily for 30 day.*[5] *With the exception of a few gross observations made in the high-dose group in the first week of the study, no adverse effects were observed.*

The short-term oral and intravenous (i.v.) toxicity studies summarized below are described in Table 9.

In 28-day gavage studies in Han-Wistar rats, dosing with 3.12 g/kg 33% Caprylic/Capric Triglyceride did not produce any signs of toxicity,[36] but undiluted test material produced some gastrointestinal effects, decreased thymic weight, caused inflammation in the lungs, and resulted in changes in some clinical pathology parameters.[37] These changes were reversible. In Göttingen minipigs, clinical signs of toxicity were observed with 0.5 and 2 ml/kg/day Caprylic/Capric Triglyceride administered by gavage; no changes in organ weights or gross or microscopic lesions were observed.[38] In rats, a no-observed adverse effect level (NOAEL) of 10 mg/kg bw/day was reported in a 30 day study with Caprylic/Capric Triglyceride,[39] and a NOAEL of 3500 mg/kg/day was reported with MLCT.[28] In a human study, no adverse effects were observed in a placebo-controlled double-blind study in which healthy subjects ingested 42 g/day MLCT.[28]

No adverse effects were observed in a study in which rabbits were given a Tripelargonin/LCT emulsion via a TPN infusion regimen for 7 h/day for 11 days.[30,40]

Subchronic Toxicity Studies

Application of a perfumed skin softener formulation containing 4% Caprylic/Capric Triglyceride to the shaved skin of female rats at a dose of 2 ml/kg 5 days/wk for 13 wks did not produce any toxic effects.[5] *No toxic effects were noted in a 3-mos feeding study of 1 and 5% Caprylic/Capric Triglyceride in the diet of rats.*

The subchronic toxicity studies summarized below are described in Table 9.

Three-month feeding studies were performed with Caprylic/Capric Triglyceride in rats[39] and dogs.[41] The NOAELs were 5% and 15%, respectively, and no toxicologically-relevant signs of toxicity were observed at the highest doses.

Chronic Toxicity Studies

No significant differences were found in growth rate or the incidence of lesions between groups of rats fed a mixture containing 0.0002% Trilaurin for 2 years and controls.[4] *In another chronic study, cardiac lipidosis and/or focal fibrosis was observed in rats fed a basal diet consisting of 30 cal % Trierucin for 24 weeks. Renal tubular dilatation, proteinaceous casts, or fibrosis were also reported. When the chronic oral toxicity of Tricaprylin was evaluated using groups of male rats, significant reductions in hematological/clinical chemistry parameters (10 ml/kg group) and significant increases in the liver (2 ml/kg) and adrenal gland weights (2 and 10 ml/kg) were noted after 26 weeks of dosing. Few lesions in the kidneys, myocardium, and aorta were noted when Tricaprylin was tested in another chronic oral toxicity study.*

In studies in which rats were fed a diet containing 19.6% of a MCT composed of about 75% caprylic acid and 25% capric acid for 47 weeks or an MCT at 20% in the diet, for 1 yr, nutritional effects resulting from long-term consumption of this ingredient were observed, but no effects were interpreted as adverse or toxic.[5]

In a 9-mos feeding study, an oil containing 64% Triheptanoin was not toxic in rats Table 9.[42]

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Tricaprylin (≤10 ml/kg) was not teratogenic in mice or rats when administered orally [4] *In another study on reproductive effects, a uterine injection on 0.1 ml Tricaprylin was effective in producing fusion of the endometrial epithelium (symplasma formation) and decidualization of the stroma in pseudopregnant New Zealand white rabbits. The oral administration of 4750 mg/kg/day Triethylhexanoin [Trioctanoin] on days 6-13 of gestation to mice did not result in any significant differences in indices of potential developmental toxicity (i.e., litter size, birth weight, and neonatal growth and survival to postnatal day 3) between test and control groups. Test results for 291 fetuses from various strains of mice injected intraperitoneally with 0.5 mmol/kg bw Triethylhexanoin [Trioctanoin; was the vehicle control in a teratogenicity study] on days 8 and 12 of gestation indicated various kinds of eye abnormalities in 6.2% of the fetuses.*

In a reproduction study, young adult male and female rats were fed a balanced diet containing 19.6% of a triglyceride of 75% caprylic and 25% capric acid for three weeks before mating.[5] *Litter size and birth weight of the test animals were*

similar to those of rats on conventional or low fat diets, but mortality during lactation was somewhat higher, and there was less weight gain due to a smaller volume of milk secreted. After weaning, the F_1 generation was fed as the F_0 generation had been and showed a weight gain comparable to that of control rats.

Tricaprylin

In a study evaluating the developmental toxicity of trichloroacetonitrile in which Tricaprylin was used as a vehicle, a possibly biologically significant effect (increased resorptions, reduced fetal weight, and anomalies) was observed in the Tricaprylin control group when compared to the water control group.[43] Therefore, the developmental toxicity of trichloroacetonitrile was reexamined using Tricaprylin and corn oil as vehicles. Groups of 20 gravid Long-Evans rats were dosed by gavage on days 6-18 of gestation with 15 mg/kg/day trichloroacetonitrile in Tricaprylin and 15-75 mg/kg/day trichloroacetonitrile in corn oil; vehicle control groups were dosed with Tricaprylin, corn oil only, and water. The dosing volume was 10 ml/kg. All dams were killed on day 20 of gestation.

Statistically significant difference in some parameters was observed in the Tricaprylin control group compared to the water and/or corn oil control groups. There was a statistically significant increase in the percent implantation loss in the Tricaprylin (only) group as compared to both the water and corn oil controls, and the total implants/litter was statistically significantly less when compared to the corn oil, but not the water, control group. Also, there were statistically significant decreases in fetal body weights and crown-rump length in the Tricaprylin control group as compared to the water and corn oil control groups. There was no statistically significant difference in the incidence of fetal anomalies among the three control groups. In the dams, the maternal average kidney weight was statistically significantly increased in the Tricaprylin controls when compared to the water and corn oil controls; no effect on liver or spleen weight was reported.

The study authors postulated that the differences observed between the Tricaprylin group and the other two control groups may be attributable to potential changes in nutritional status. Dams of the Tricaprylin group gained significantly less weight than those of the corn oil group during days 15-18 of gestation. However, food and water consumption were not monitored. The study authors also stated that the differences in reproductive parameters could be due to normal variation for Long-Evans rats.

Additionally, the developmental toxicity of trichloroacetonitrile appeared to be vehicle-dependent; developmental effects caused by trichloroacetonitrile were seen at higher doses when administered in corn oil compared to those seen when Tricaprylin was used as the vehicle. The study authors suggested that trichloroacetonitrile and Tricaprylin "appear to interact in some way to potentiate effects of the cardiovascular system." The adverse effects of trichloroacetonitrile in Tricaprylin were seen at doses as low as 1 mg/kg/d and included a number of different kinds of heart defects.

GENOTOXICITY STUDIES

In Vitro

Ames test results indicated that Trihydroxystearin was not mutagenic to the following Salmonella typhimurium strains, with or without metabolic activation, when tested at concentrations ranging from 3 to 1000 µg/plate: TA1535, TA1537, TA1538, TA98, and TA100.[1]

In the Ames test, Tricaprylin was mutagenic in one of four S. typhimurium strains tested.[4] *Negative test results were reported for Trilaurin in the following assays: dominant lethal test, host-mediated mitotic gene conversion assay, chromosomal aberrations assay, micronucleus test, sister chromatid exchange (SCE) assay, spot test for gene mutations, and cytogenetic assay for clastogenic activity. In the Ames test, Trilaurin, Triethylhexanoin [Trioctanoin], Triolein, Tristearin, and Triisostearin were not mutagenic in S. typhimurium strains. However, Triethylhexanoin [Trioctanoin] was mutagenic in the spot test for gene mutations. In other tests, no clastogenic activity was noted when Triethylhexanoin [Trioctanoin] was tested in a cytogenetics assay and results were negative in a sister chromatid exchanges mutagenicity assay.*

The genotoxicity studies summarized below are described in Table 10.

Tristearin (5000 µg/plate)[32] and Tricaprylin (concentration not stated)[35] were not mutagenic in the Ames test, Triethylhexanoin was not genotoxic in an Ames test (50-5000 µg/plate) or a mammalian chromosomal aberration assay (7.5-4000 µg/ml),[25] and Triisononanoin was not genotoxic in an Ames test (50-5000 µg/plate), chromosomal aberration assay (10-320 µg/ml), or a mammalian cell gene mutation assay (5-80 µg/ml).[44]

A lipid emulsion that comprises a mixture of soybean oil, Caprylic/Capric Triglyceride, olive oil, and fish oil (test concentrations not provided) was not genotoxic in an Ames test, a chromosomal aberration assay, or a hypoxanthine phosphoribosyl transferase (HPRT) gene mutation assay.[27] In vivo, the emulsion was not genotoxic in a bone marrow cytogenic study in rats.

CARCINOGENICITY STUDIES

Following intraperitoneal injection of 0.25 ml Tricaprylin into 30 female mice in a tumorigenicity study, lung tumors were observed in 37% of the animals.[4] *In the untreated-control group of 30 mice, the lung tumor incidence was 23%. The results of an oral carcinogenicity study by the National Toxicology Program (NTP) indicated that Tricaprylin caused a statistically significant dose-related increase in the incidence of pancreatic acinar cell hyperplasia and adenoma in rats. Tricaprylin did*

not induce acinar cell carcinomas. Additionally, the incidence of squamous cell papilloma in the squamous portion of the stomach of rats in the highest dose group (10 ml/kg Tricaprylin) was significantly greater when compared to controls.

ANTI-CARCINOGENICITY STUDIES

Trilaurin (dose not specified) completely inhibited the formation of neoplasms initiated by 7,12-dimethylbenz[a]anthracene (DMBA) and promoted by croton oil.[4] *Additionally, extensive damage to tumor cells (lymphoma implants in the liver) was noted in rats after oral dosing with Tricaprylin.*

DERMAL IRRITATION AND SENSITIZATION STUDIES

Trihydroxystearin was not irritating to the skin of albino rabbits in 24-hour occlusive patch tests.[1] *In 48-hour occlusive patch tests, Trihydroxystearin did not induce skin irritation in any of the 103 subjects tested.*

Undiluted Triisostearin and a 20% solution of Tribehenin (0.5 ml) in liquid paraffin were, at most, mildly irritating when applied to the skin of rabbits.[4] *Undiluted Triethylhexanoin [Trioctanoin] and an eyeliner containing 36.3% Trilaurin did not induce cutaneous irritation in rabbits. Neither Tribehenin (test concentration not provided) nor Triethylhexanoin [Trioctanoin; 1% intradermal induction, 100% occlusive topical induction; 25% occlusive challenge] induced sensitization in the Magnusson-Kligman guinea pig maximization test. Triisostearin (o.02 ml/cm^2) did not induce significant cutaneous reactions in a study evaluating the phototoxicity and photoallergenicity potential of this ingredient in guinea pigs.*

An eyeliner containing 36.3% Trilaurin did not induce skin irritation reactions in 91 test subjects.[4] *Triethylhexanoin [Trioctanoin; details not provided] did not induce skin irritation in 25 subjects. A lip enhancer cream containing 0.38% Tribehenin was not comedogenic and did not induce clinically significant skin irritation in any of the 18 subjects evaluated in a 28-day test. Repeated insult patch test (RIPT) results (occlusive patches) for the following products were negative: eye enhancer cream containing 0.32% Tribehenin (198 subjects), hand cream containing 0.38% Tribehenin (at least 200 subjects), lip cream containing 0.38% Tribehenin (at least 200 subjects), and an eye defining pencil containing 1.68% Tristearin. None of these products induced clinically significant irritant or allergic contact dermatitis. In a skin sensitization test involving 91 subjects, there was no evidence of delayed contact hypersensitivity after repeated applications (occlusive patches) of an eyebrow pencil containing 40% Trilaurin. Also, Triethylhexanoin [Trioctanoin; details not provided] did not induce sensitization in a contact allergy test.*

Application of a perfumed skin softener formulation containing 4% Caprylic/Capric Triglyceride to the shaved skin of female rats at a dose of 2 ml/kg 5 days/wk for 13 wks did not result in any localized skin effects. Caprylic/Capric Triglyceride was not a sensitizer in guinea pigs. Undiluted Caprylic/Capric Triglyceride was not irritating when tested using groups of 12 (21-day patch test), or 40 (test methods not described), and it was not an irritant or sensitizer in 128, subjects (Draize repeated insult patch test).

The dermal irritation and sensitization studies summarized below are described in Table 11.

Dermal effects were observed in 4-h semi-occlusive patch tests in rabbits with undiluted Triheptanoin; very slight to slight erythema was reported in 1-2 of 3 animals in one study, but in the other study, very slight to well-defined erythema was observed in all 6 animals 30-60 min after patch removal, moderate to severe erythema and severe edema, discoloration, and dryness with sanguineous lacerations and scaling was observed in 1 animal 24-72 h after dosing, and scaling was observed in all animals at day 6.[31] Triisostearin (test concentration not provided) produced well-defined erythema in all 3 rabbits at 1 and 24 h; all erythema was resolved by 72 h.[33] No irritation was observed in 4-h patch tests with undiluted Tristearin,[32] Caprylic/Capric Triglyceride,[39] or C8-C12 Acid Triglycerides.[39] Triheptanoin (100%)[31] and Tristearin (50%)[32] were not sensitizers in guinea pigs. Triisononanoin was predicted to be non-irritating in an EpiSkin™ in vitro test.[44] However, in a mouse local lymph node assay (LLNA), it was predicted that Triisononanoin may cause sensitization; results were negative with 25% and 50% Triisononanoin, but positive when tested at 100%.[44]

A facial oil containing 95.51% Caprylic/Capric Triglyceride was not an irritant is a 24-h single insult occlusive patch test in 17 human subjects,[45] and it was not a sensitizer in a human modified maximization patch test with 26 subjects.[46] In human repeated insult patch tests, a moisturizer containing 6% Tribehenin was not a sensitizer (102 subjects),[47] and a mixture containing 20% Tribehenin had no clinically significant potential for dermal irritation or sensitization (52 subjects).[48] Triolein was not a sensitizer in a chamber test; details were not provided.[35]

PHOTOSENSITIZATION

Caprylic/Capric Triglyceride

The photosensitization potential of a facial cream oil containing 95.51% Caprylic/Capric Triglyceride was evaluated in a RIPT photocontact allergenicity assay completed in 27 subjects.[49] For induction, an occlusive patch consisting of 40 mg of the test material spread uniformly onto a 2 x 2 cm (10 mg/cm^2) cotton cloth was applied to the lower back of each subject for 24 h; immediately following patch removal, the test site was exposed to two minimal erythema doses (MEDs) from a xenon arc solar simulator. This procedure was repeated 2x/wk for 3 wks, for a total of 6 induction applications. The light source was a 150 W compact xenon arc solar simulator (Solar Light Company) equipped with a UV-reflecting dichroic mirror and a 1 mm thick Schott WG320 filter; a 1 mm thick UG11 filter was also used. The solar spectrum (SSR waveband) was used to

determine the individual MED. The size of the irradiated field at skin level was approximately a 1cm diameter circle. Total irradiance at skin level was 90.0 mW/cm2. The UVA intensity was 52.5 mW/cm^2.

Following a 10-day non-treatment period, a challenge patch was applied for 24 h to a previously untreated site on the opposite side of the back, followed by exposure to ½ MED of solar simulated radiation plus 4 J/cm2 of UVA. (For the challenge, a 1 mm thick Schott WG-345 filter was added to eliminate the UVB component (290-320 nm) and to produce a continuous broadband UVA extending from 320 to 410nm.) An unirradiated site treated with the test product served as a "dark" control. The sites were examined at 48 and 72 hours after irradiation for evidence of photocontact sensitization. The facial oil containing 95.51% Caprylic/Capric Triglyceride did not possess a detectable photocontact-sensitizing potential in human skin.

OCULAR IRRITATION STUDIES

Trihydroxystearin was classified as a mild, transient ocular irritant in albino rabbits.[1]

An eye enhancer cream containing 0.32% Tribehenin and a hand cream containing 0.38% Tribehenin were classified as non-irritants in an in vitro chorioallantoic membrane vascular assay for determining the ocular irritation potential of chemicals.[4] *An eyeliner containing 36.3% Trilaurin and a 20% solution of Tribehenin in liquid paraffin were, at most, mildly irritating to the eyes of rabbits. Triethylhexanoin [Trioctanoin] and Triisostearin did not induce ocular irritation in rabbits.*

An eye enhancer cream containing 0.32% Tribehenin induced reactions ranging from mild to moderate ocular irritation in a group of 20 subjects, which resolved to either mild irritation or no irritation reactions at 2 hours post exposure.[4] *In a clinical in-use safety test of two eye enhancer creams containing 0.32% Tribehenin, neither ocular irritation nor clinically relevant alterations in visual acuity were observed after 4 consecutive weeks of daily product use. Similar results were reported after testing of another eye enhancer cream containing 0.32% Tribehenin and an eye defining pencil containing 1.68% Tristearin in separate studies according to the same procedure. All of the subjects tested in these studies were contact lens wearers*.

Caprylic/Capric Triglyceride was non-irritating, to at most very mildly irritating, to rabbit eyes.[5]

The ocular irritation studies summarized below are described in Table 12.

Undiluted Triheptanoin,[31] Tristearin,[32] Caprylic/Capric Triglyceride,[39] and C8-12 Acid Triglyceride,[39] as well as Triisostearin at an unspecified concentration,[33] were not irritating in rabbit eyes. Triisononanoin was predicted to be non-irritating in an in vitro eye irritation test using the SkinEthic™ reconstructed model.[44]

SUMMARY

In 2000, the Panel assessed the safety of Trihydroxystearin and concluded that, based on the available animal and clinical data, which included summary data from the CIR safety assessments of Hydroxystearic Acid and Glyceryl Stearate and Glyceryl Stearate SE, Trihydroxystearin is safe as used in cosmetics. The Panel published two additional reports on related ingredients; the Panel concluded that Caprylic/Capric Triglyceride (1980) and Trilaurin and 22 additional glyceryl triesters (2001) are safe as used in cosmetics. An additional 29 triglycerides that are cosmetic ingredients and have not been reviewed by the Panel have also been identified. This safety assessment is a compilation of these 51 triglycerides, most of which (but not all) function as skin conditioning agents and/or viscosity increasing agents in cosmetics.

Some of these triglycerides are produced synthetically via classical Fischer type esterification methods, although the reaction may be promoted by acid or base catalysis, or by the use of an acid chloride. Additionally, some of these ingredients may be natural sourced and produced by transesterification.

Thirty-one of the 51 ingredients included in this safety assessment are in use, and Caprylic/Capric Triglyceride has the highest frequency of use (6000 formulations). According to the results of a concentration of use survey conducted by the Council, Triethylhexanoin has the highest maximum use concentration, with concentrations of 100% reported for face and neck formulations and 63% in lipstick formulations.

Approximately half of the ingredients included in this safety assessment have been reviewed previously by the Panel. The frequency and maximum concentrations of use for the majority of these ingredients have generally increased since these ingredients were originally reviewed.

Many of the triglycerides are approved by the FDA for use as direct or indirect food additives.

Oral absorption and metabolism of foods containing LCT mixtures differ from those containing Caprylic/Capric Triglyceride. C > 12 are degraded by salivary, intestinal and pancreatic lipases into two fatty acids and a monoacyl glycerol, whereas, Caprylic/Capric Triglyceride is degraded by the same enzymes into three fatty acids and the simple glycerol backbone.

In newborn Rhesus monkeys administered a single dose of Tripelargonin or Triethylhexanoin via NG tube, free fatty acid concentrations and ketone 3HB increased with time. In New Zealand male rabbits given a Tripelargonin/LCT emulsion via a TPN infusion regimen 7 h/day for 11 days, 3HB concentrations were significantly decreased and plasma concentrations of short-chain fatty acids were significantly increased.

In acute toxicity testing, the dermal LD_{50} in rats was > 2 g/kg (the highest dose tested) for both Triheptanoin and Tristearin. The oral LD_{50} was > 2 g/kg for Triisostearin in mice and rats, > 2 g/kg Triolein in mice, > 5 g/kg Triheptanoin in mice, and > 48 g/kg Triethylhexanoin in rats. The oral LD_{50} of a MLCT oil was > 5 g/kg in rats. A single dose of 8.4 ml/kg bw Tripelargonin and Triethylhexanoin, administered via NG tube, did not affect activity level or induce narcolepsy in newborn Rhesus monkeys.

In 28-day gavage studies in Han-Wistar rats, dosing with 33% Caprylic/Capric Triglyceride did not produce any signs of toxicity, but undiluted test material produced some gastrointestinal effects, decreased thymic weight, caused inflammation in the lungs, and resulted in changes in some clinical pathology parameters. These changes were reversible. In Göttingen mini-pigs, clinical signs of toxicity were observed with 0.5 and 2 ml/kg/day Caprylic/Capric Triglyceride administered by gavage; no changes in organ weights or gross or microscopic lesions were observed. No adverse effects were observed in a study in which rabbits were given a Tripelargonin/LCT emulsion via a TPN infusion regimen for 7 h/day for 11 days

Short-term and subchronic feeding studies were conducted with Caprylic/Capric Triglyceride. In rats, a NOAEL of 10 mg/kg bw/day was reported in a 30 day study with Caprylic/Capric Triglyceride, and a NOAEL of 3500 mg/kg/day was reported with mixture of triglycerides with alkyl chain lengths C8-C24. In a human study, no adverse effects were observed in a placebo-controlled double-blind study in which healthy subjects ingested 42 g/day of the C8-C24 mixture. Three-month feeding studies were performed with Caprylic/Capric Triglyceride in rats and dogs, and the NOAELs were 5% and 15%, respectively; no toxicologically-relevant signs of toxicity were observed at the highest doses.

In a chronic (9-mos) feeding study, an oil containing 64% Triheptanoin was not toxic in rats.

Tricaprylin was used as a vehicle in an oral (gavage) DART study of trichloroacetonitrile, and its effect on the test results was compared to other vehicles. Additionally, the potential developmental toxicity of Tricaprylin was evaluated in comparison to the two other vehicles (water and corn oil). There was a statistically significant increase in the percent implantation loss in the Tricaprylin group as compared to both the water and corn oil controls, and the total implants/litter was statistically significantly less when compared to the corn oil, but not the water, control group. Also, there were statistically significant decreases in fetal body weights and crown-rump length in the Tricaprylin control group as compared to the water and corn oil control groups. The study authors postulated that the differences observed between the Tricaprylin group and the other two control groups may be attributable to potential changes in nutritional status.

Additionally, the developmental toxicity of trichloroacetonitrile appeared to be vehicle-dependent; developmental effects caused by trichloroacetonitrile were seen at higher doses when administered in corn oil compared to those seen when Tricaprylin was used as the vehicle. The study authors suggested that trichloroacetonitrile and Tricaprylin "appear to interact in some way to potentiate effects of the cardiovascular system."

The genotoxicity of several triglycerides was evaluated, and all the results were negative. Tristearin (5000 µg/plate) and Tricaprylin (concentration not stated) were not mutagenic in the Ames test, Triethylhexanoin was not genotoxic in an Ames test (50-5000 µg/plate) or a mammalian chromosomal aberration assay (7.5-4000 µg/ml), and Triisononanoin was not genotoxic in an Ames test (50-5000 µg/plate), chromosomal aberration assay (10-320 µg/ml), or a mammalian cell gene mutation assay (5-80 µg/ml).

A lipid emulsion that comprises a mixture of soybean oil, Caprylic/Capric Triglyceride, olive oil, and fish oil (test concentrations not provided) was not genotoxic in an Ames test, a chromosomal aberration assay, or a hypoxanthine phosphoribosyl transferase (HPRT) gene mutation assay. In vivo, the emulsion was not genotoxic in a bone marrow cytogenic study in rats.

Mixed results were obtained in dermal irritation and sensitization studies. Dermal effects were observed in 4-h semi-occlusive patch tests in rabbits with undiluted Triheptanoin; very slight to slight erythema was reported in 1-2 of 3 animals in one study, but in the other, very slight to well-defined erythema was observed in all 6 animals 30-60 min after patch removal, moderate to severe erythema and severe edema, discoloration, and dryness with sanguineous lacerations and scaling was observed in 1 animal 24-72 h after dosing, and scaling was observed in all animals at day 6. Triisostearin (test concentration not provided) produced well-defined erythema in all 3 rabbits at 1 and 24 h; all erythema was resolved by 72 h. No irritation was observed in 4-h patch tests with undiluted Tristearin, Caprylic/Capric Triglyceride, or C8-C12 Acid Triglycerides. Triheptanoin (100%) and Tristearin (50%) were not sensitizers in guinea pigs. Triisononanoin was predicted to be non-irritating in an EpiSkin™ in vitro test. However, in a mouse LLNA, it was predicted that Triisononanoin may cause sensitization; results were negative with 25% and 50% Triisononanoin but positive when tested at 100%.

In human testing, a facial oil containing 95.51% Caprylic/Capric Triglyceride was not an irritant is a 24-h single insult occlusive patch test in 17 subjects, was not a sensitizer in a human modified maximization patch test with 26 subjects, and was not a photosensitizer. In HRIPTs, a moisturizer containing 6% Tribehenin was not a sensitizer (102 subjects), and a mixture containing 20% Tribehenin had no clinically significant potential for dermal irritation or sensitization (52 subjects). Triolein was not a sensitizer in a chamber test; details were not provided.

Several triglycerides were evaluated and found not to be ocular irritants. Undiluted Triheptanoin, Tristearin, Caprylic/Capric Triglyceride, and C8-12 Acid Triglyceride, as well as Triisostearin at an unspecified concentration, were not irritating in

rabbit eyes. Triisononanoin was predicted to be non-irritating in an in vitro eye irritation test using the SkinEthic™ reconstructed model.

No new carcinogenicity data were discovered in an extensive search of the published literature.

DISCUSSION

In accordance with its procedures, the CIR evaluates the conclusions of previously-issued reports every 15 years. The Panel has issued three final reports on the safety of 25 triglycerides (i.e., fatty acid triesters of glycerin) in the past 15+ years. The Panel previously concluded that Trihydroxystearin (2000), Caprylic/Capric Triglyceride (1980; reaffirmed in 2003), and a family of ingredients that included Trilaurin and 22 additional glyceryl triesters (2001) are safe as used in cosmetics. Additionally, the Panel determined that it was appropriate to include 26 triglycerides that have not yet been reviewed. The collection of these ingredients in one report enables the assembly of reinforcing and complementary test data. Safety profiles of these ingredients are consistent with roles of most constituents as dietary components and safe conclusions in previous reports.

Upon initial review of the safety of the triglycerides as used in cosmetics at its April 10-11, 2017 meeting, the Panel determined additional data were needed to assess the safety of these ingredients and issued an Insufficient Data Announcement (IDA). Many, but not all, of the data requests were satisfied.

The main focus of the IDA was for irritation and sensitization data at concentration of use on four ingredients (i.e., Tribehenin, Caprylic/Capric Triglyceride, Triethylhexanoin, and C10-40 Isoalkyl Acid Triglyceride). Data were received for two of the four ingredients (i.e., Tribehenin and Caprylic/Capric Triglyceride), and the Panel acknowledged the negative results obtained in a guinea pig maximization study (1% intradermal induction, 100% occlusive topical induction; 25% occlusive challenge) that was reported in the previous (2001) report. Although data were not received on all four ingredients included in the IDA, the Panel stated that the weight of the evidence supported the safety of all the ingredients included in this report, and therefore their data needs were satisfied.

Approximately half of the ingredients in this safety assessment have been reviewed previously by the Panel. The frequency and maximum concentrations of use for the majority of these ingredients has increased when compared to the original review. The most remarkable increase is in the frequency of use of Caprylic/Capric Triglyceride; in 2003, this ingredient was reported to be used in 763 formulations and in 2017, it is reported to be used in 6000 formulations. Also, in 2003, the maximum leave-on concentration of use for Caprylic/Capric Triglyceride was 84%, it is now reported to 95.6% in face and neck products.

One reported possible function of Docosahexenoic/Docosapentenoic/Oleic/Palmitic Triglyceride is skin bleaching agent. In the United States, skin bleaching agent is not considered a cosmetic function, and therefore use in that manner is not being assessed in this report.

During its original review of Trilaurin and other glyceryl triesters, the Panel noted that, as part of an effort to evaluate vehicles used in carcinogenicity studies, the NTP conducted a 2-year carcinogenicity study in rats given Tricaprylin by gavage. This treatment was associated with a statistically significant dose-related increase in pancreatic acinar cell hyperplasia and adenoma, but there were no acinar carcinomas, the incidence of mononuclear leukemia was less, and nephropathy findings were reduced, compared to corn oil controls. In a tumor inhibition study, Trilaurin was found to inhibit the formation of neoplasms initiated by DMBA and promoted by croton oil. However, the Panel stated that no restrictions were warranted for any of these ingredients.

High purity is needed for the triglycerides. In 2007, the Panel published a final report on a diglycerides, and concluded that the ingredients in the diglyceride family are safe in the present practices of use and concentration provided the content of 1,2-diesters is not high enough to induce epidermal hyperplasia. The Panel discussed that there was an increased level of concern because of data regarding the induction of protein kinase C (PKC) and the tumor promotion potential of 1,2-diacylglycerols. The Panel noted that, nominally, glyceryl-1,3-diesters contain 1,2-diesters, raising the concern that 1,2-diesters could potentially induce hyperplasia. The Panel did note that these compounds are more likely to cause these effects when the fatty acid chain length is ≤14 carbons, when one fatty acid is saturated and one is not, and when given at high doses, repeatedly.

Based on existing information from a previous CIR safety assessment, minimal percutaneous absorption of Triolein has been demonstrated in vivo using guinea pigs (but not hairless mice), and in vitro using full-thickness skin from hairless mice. However, the Panel recognized that, reportedly, Triolein and Tricaprylin can enhance the skin penetration of other chemicals, and the Panel cautioned that care should be taken in formulating cosmetic products that may contain these ingredients in combination with any ingredients whose safety was based on their lack of dermal absorption data, or when dermal absorption was a concern.

The Panel acknowledged that some of the triglycerides may be formed from plant-derived or animal-derived constituents. The Panel thus expressed concern regarding pesticide residues and heavy metals that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use the necessary procedures to sufficiently limit amounts of such impurities in an ingredient before blending them into cosmetic formulations. Additionally, the Panel considered the risks inherent in using animal-derived ingredients, namely the transmission of infectious agents. Although tallow may be used in

the manufacture of Cod Liver/Mink/Tallow Triglyceride and is clearly animal-derived, the Panel notes that tallow is highly processed, and tallow derivatives even more so. The Panel agrees with determinations by the U.S. FDA that tallow derivatives are not risk materials for transmission of infectious agents.

Finally, the Panel discussed the issue of incidental inhalation exposure, as some of the triglycerides are used in cosmetic sprays and could possibly be inhaled. For example, Triethylhexanoin and Triisostearin are reported to be used at maximum concentrations of 36% and 30%, respectively, in perfumes, and 14.7% and 10.4%, respectively, in face powders. The Panel noted that in aerosol products, 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings

CONCLUSION

The CIR Expert Panel concluded that the following 51 triglycerides are safe in cosmetics in the present practices of use and concentration described in this safety assessment:

Acetic/Linoleic/Palmitic Triglyceride*
C12-18 Acid Triglyceride
C18-36 Acid Triglyceride
C8-12 Acid Triglyceride*
Capric/Lauric/Myristic/Oleic Triglyceride*
Caprylic/Capric Triglyceride
Caprylic/Capric/Lauric Triglyceride
Caprylic/Capric/Linoleic Triglyceride
Caprylic/Capric/Myristic/Stearic Triglyceride
Caprylic/Capric/Palmitic/Stearic Triglyceride*
Caprylic/Capric/Stearic Triglyceride
C10-40 Isoalkyl Acid Triglyceride
Cod Liver/Mink/Tallow Triglyceride*
C10-18 Triglycerides
Docosahexenoic/Docosapentenoic/Oleic/Palmitic Triglyceride*
Glyceryl Stearate Diacetate*
Glyceryl Triacetyl Hydroxystearate
Glyceryl Triacetyl Ricinoleate
Glyceryl Tri-Hydrogenated Rosinate
Glyceryl Tripalmate/Palm
Kernelate/Olivate/Macadamiate/Rapeseedate*
Hydrogenated C12-18 Triglycerides
Isomerized Safflower Glycerides*
Jojoba Oil/Caprylic/Capric Triglyceride Esters*
Lauric/Palmitic/Oleic Triglyceride*
Oleic/Linoleic Triglyceride*
Oleic/Palmitic/Lauric/Myristic/Linoleic Triglyceride*
Palmitic/Stearic Triglyceride
Ricinoleic/Caproic/Caprylic/Capric Triglyceride*
Triarachidin*
Tribehenin
Tricaprin
Tricaprylin
Tierucin*
Triethylhexanoin
Triheptanoin
Triheptylundecanoin*
Trihydroxystearin
Triisononanoin
Triisopalmitin*
Triisostearin
Trilaurin
Trilinolein
Trilinolenin
Trimyristin
Triolein
Tripalmitin
Tripalmitolein*
Tripelargonin*
Triricinolein*
Tristearin
Triundecanoin

*Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.

TABLES

Table 1. Triglycerides included in this report

Acetic/Linoleic/Palmitic Triglyceride	Glyceryl Triacetyl Ricinoleate	Triheptanoin
C8-12 Acid Triglyceride	Glyceryl Tri-Hydrogenated Rosinate	Triheptylundecanoin
C12-18 Acid Triglyceride	Glyceryl Tripalmate/Palm Kernelate/	Trihydroxystearin
C18-36 Acid Triglyceride	Olivate/Macadamiate/Rapeseedate	Triisononanoin
Capric/Lauric/Myristic/Oleic Triglyceride	Hydrogenated C12-18 Triglycerides	Triisopalmitin
Caprylic/Capric Triglyceride	Isomerized Safflower Glycerides	Triisostearin
Caprylic/Capric/Lauric Triglyceride	Jojoba Oil/Caprylic/Capric Triglyceride Esters	Trilaurin
Caprylic/Capric/Linoleic Triglyceride	Lauric/Palmitic/Oleic Triglyceride	Trilinolein
Caprylic/Capric/Myristic/Stearic Triglyceride	Oleic/Linoleic Triglyceride	Trilinolenin
Caprylic/Capric/Palmitic/Stearic Triglyceride	Oleic/Palmitic/Lauric/Myristic/Linoleic Triglyceride	Trimyristin
Caprylic/Capric/Stearic Triglyceride	Palmitic/Stearic Triglyceride	Triolein
C10-40 Isoalkyl Acid Triglyceride	Ricinoleic/Caproic/Caprylic/Capric Triglyceride	Tripalmitin
Cod Liver/Mink/Tallow Triglyceride	Triarachidin	Tripalmitolein
C10-18 Triglycerides	Tribehenin	Tripelargonin
Docosahexenoic/Docosapentenoic/	Tricaprin	Triricinolein
Oleic/Palmitic Triglyceride	Tricaprylin	Tristearin
Glyceryl Stearate Diacetate	Trierucin	Triundecanoin
Glyceryl Triacetyl Hydroxystearate	Triethylhexanoin (previously, Trioctanoin)	

Note: ingredients that were previously reviewed are indicated in blue

Table 2. Definitions, idealized structures, and functions of the ingredients in this safety assessment. [7;[CIR Staff]]

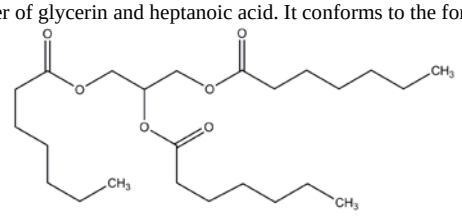
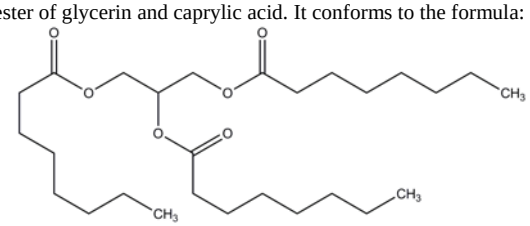
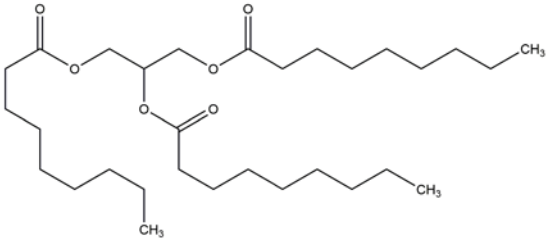
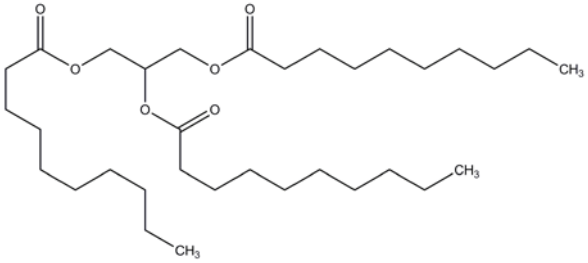
Ingredient/CAS No.	Definition & Structure	Function(s)
	Linear chain saturated triglycerides	
Triheptanoin 620-67-7	Triheptanoin is the triester of glycerin and heptanoic acid. It conforms to the formula 	skin conditioning agent – occlusive; viscosity increasing agent – nonaqueous
Tricaprylin 538-23-8	Tricaprylin is the triester of glycerin and caprylic acid. It conforms to the formula: 	fragrance ingredient; skin conditioning agent – occlusive
Tripelargonin 126-53-4	Tripelargonin is the organic compound that conforms to the formula: 	skin conditioning agent – emollient
Tricaprin 621-71-6	Tricaprin is the triester of glycerin and capric acid. It conforms to the formula: 	fragrance ingredient; skin conditioning agent – occlusive

Table 2. **Definitions, idealized structures, and functions of the ingredients in this safety assessment.** [7;[CIR Staff]]

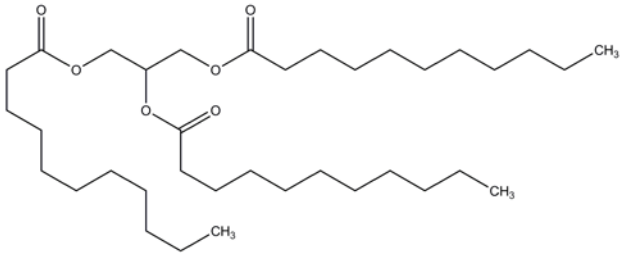
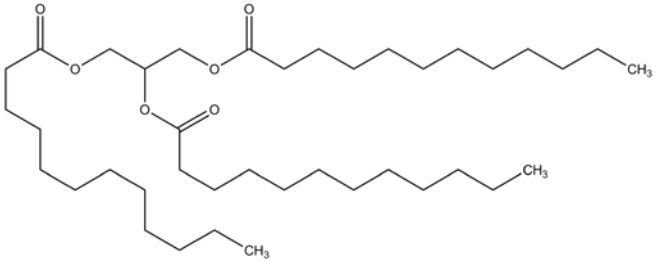
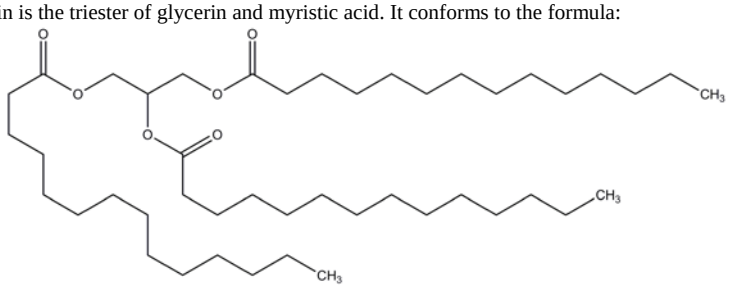
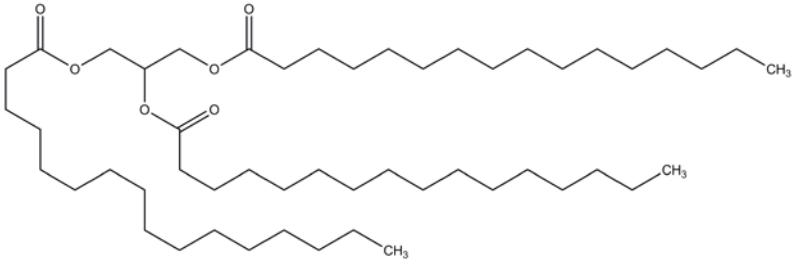
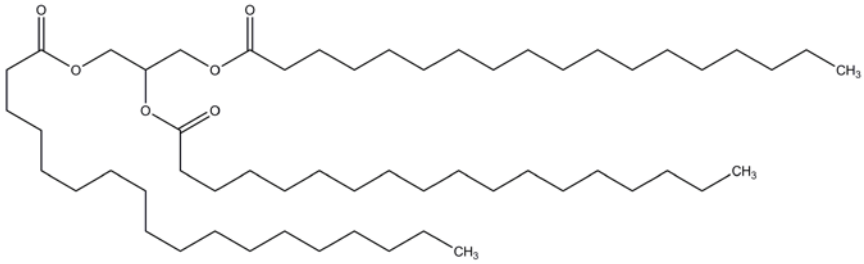
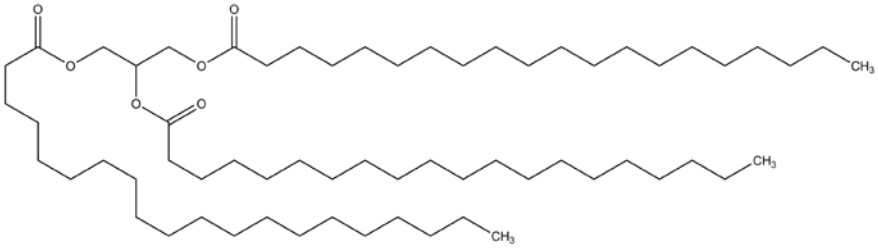
Ingredient/CAS No.	Definition & Structure	Function(s)
Triundecanoin 13552-80-2	Triundecanoin is the triester of glycerin and undecanoic acid. It conforms to the formula: 	hair conditioning agent; skin conditioning agent – occlusive
Trilaurin 538-24-9	Trilaurin is the triester of glycerin and lauric acid. It conforms to the formula: 	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Trimyristin 555-45-3	Trimyristin is the triester of glycerin and myristic acid. It conforms to the formula: 	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Tripalmitin 555-44-2	Tripalmitin is the triester of glycerin and palmitic acid. It conforms to the formula: 	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Tristearin 555-43-1	Tristearin is the triester of glycerin and stearic acid. It conforms to the formula: 	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Triarachidin 620-64-4	Triarachidin is the triester of glycerin and arachidic acid. It conforms to the formula: 	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous

Table 2. **Definitions, idealized structures, and functions of the ingredients in this safety assessment.** [7;[CIR Staff]]

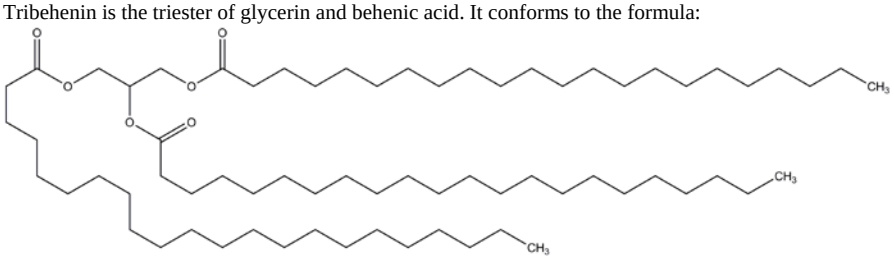
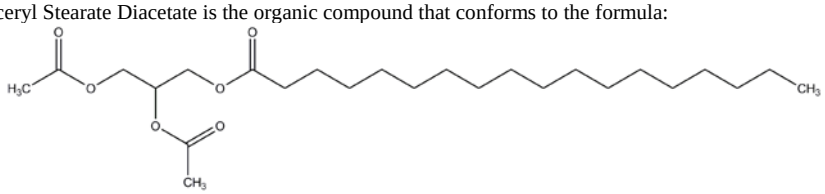
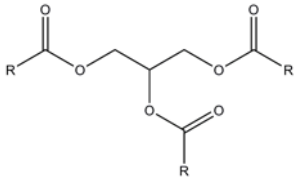
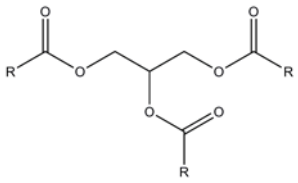
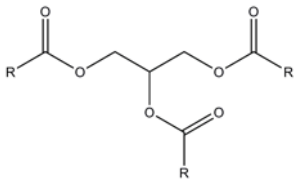
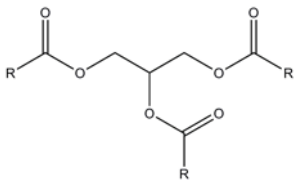
Ingredient/CAS No.	Definition & Structure	Function(s)
Tribehenin 18641-57-1	Tribehenin is the triester of glycerin and behenic acid. It conforms to the formula: 	skin conditioning agent – occlusive
	Linear, mixed chain length saturated triglycerides	
Glyceryl Stearate Diacetate 84931-78-2	Glyceryl Stearate Diacetate is the organic compound that conforms to the formula: 	skin conditioning agent – occlusive; viscosity increasing agent – nonaqueous
Caprylic/Capric Triglyceride 65381-09-1 73398-61-5	Caprylic/Capric Triglyceride is the mixed triester of glycerin and caprylic and capric acids.  [wherein RC(O)- is the residue of caprylic (C8) or capric (C10) acid.]	fragrance ingredient; skin conditioning agent – occlusive; solvent
Caprylic/Capric/Lauric Triglyceride 123465-33-8	Caprylic/Capric/Lauric Triglyceride is the mixed triester of glycerin with caprylic, capric and lauric acids.  [wherein RC(O)- is the residue of caprylic (C8), capric (C10), or lauric (C12) acid.]	skin conditioning agent – occlusive
C8-12 Acid Triglyceride	C8-12 Acid Triglyceride is the triester of glycerin and a mixture of saturated acids containing 8 to 12 carbons in the alkyl chain.  [wherein RC(O)- is the residue of a fatty acid 8, 10, or 12 carbons in length]	skin conditioning agent – occlusive; solvent; viscosity increasing agent - nonaqueous
Caprylic/Capric/Myristic/Stearic Triglyceride	Caprylic/Capric/Myristic/Stearic Triglyceride is the mixed triester of glycerin with caprylic, capric, myristic and stearic acids.  [wherein RC(O)- is the residue of caprylic, capric, myristic or stearic acid.]	skin conditioning agent – occlusive

Table 2. Definitions, idealized structures, and functions of the ingredients in this safety assessment. [7;[CIR Staff]]

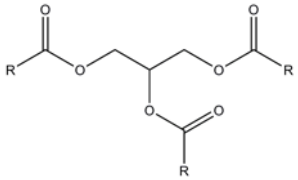
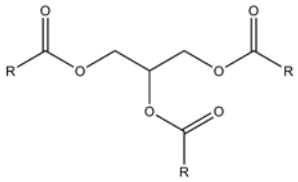
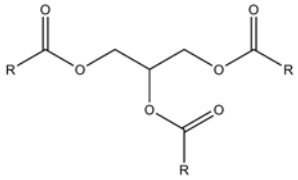
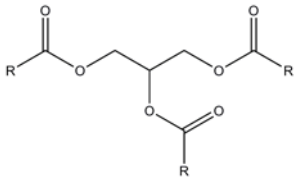
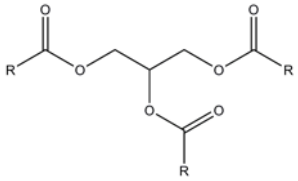
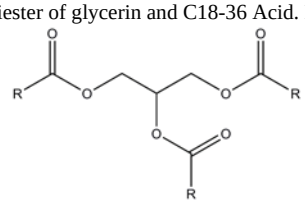
Ingredient/CAS No.	Definition & Structure	Function(s)
Caprylic/Capric/Palmitic/ Stearic Triglyceride	Caprylic/Capric/Palmitic/Stearic Triglyceride is the mixed triester of glycerin with caprylic, capric, palmitic and stearic acids.  [wherein RC(O)- is the residue of caprylic, capric, palmitic or stearic acid.]	skin conditioning agent – occlusive
Caprylic/Capric/Stearic Triglyceride	Caprylic/Capric/Stearic Triglyceride is the mixed triester of glycerin with caprylic, capric and stearic acids.  [wherein RC(O)- is the residue of caprylic, capric, or stearic acid.]	skin conditioning agent – occlusive
C10-18 Triglycerides 85665-33-4	C10-18 Triglycerides is the triester of glycerin and a mixture of normal and branched chain C10-18 fatty acids.  [wherein RC(O)- is the residue of a fatty acid 10, 12, 14, 16, or 18 carbons in length]	skin conditioning agent – occlusive; solvents
C12-18 Acid Triglyceride	C12-18 Acid Triglyceride is the triester of glycerin and a synthetic mixture of saturated acids containing 12 to 18 carbons in the alkyl chain.  [wherein RC(O)- is the residue of a fatty acid 12, 14, 16, or 18 carbons in length]	skin conditioning agent – occlusive; solvent; viscosity increasing agent - nonaqueous
Palmitic/Stearic Triglyceride	Palmitic/Stearic Triglyceride is the triester of glycerin with a mixture of palmitic and stearic acids  [wherein RC(O)- is the residue of palmitic or stearic acid]	viscosity increasing agent - nonaqueous
C18-36 Acid Triglyceride 91052-08-3	C18-36 Acid Triglyceride is the triester of glycerin and C18-36 Acid. It conforms to the formula  [wherein RC(O)- is the residue of a fatty acid 18, 20, 22, 24, 26, 28, 30, 32, 34, or 36 carbons in length]	skin conditioning agent – occlusive

Table 2. **Definitions, idealized structures, and functions of the ingredients in this safety assessment.** [7;[CIR Staff]]

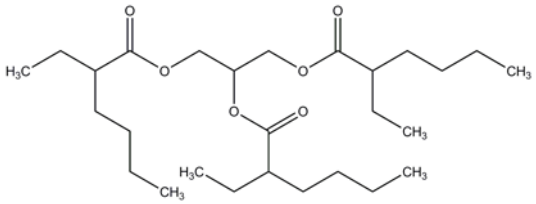
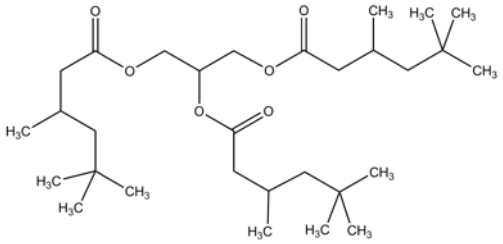
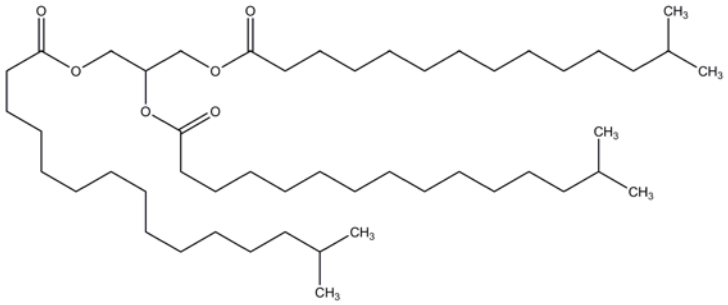
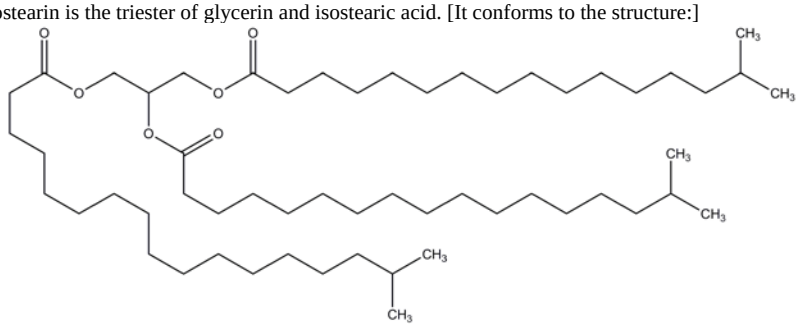
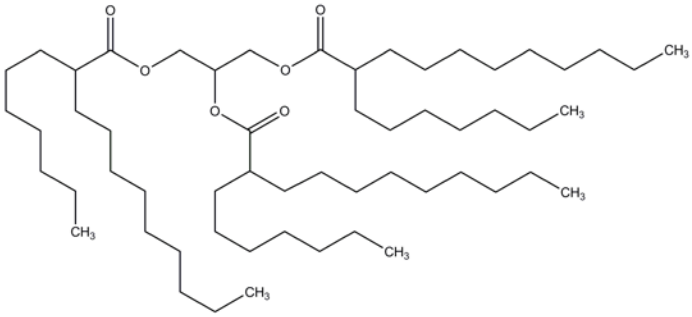
Ingredient/CAS No.	Definition & Structure	Function(s)
	Branched chain triglycerides	
Triethylhexanoin (previously named Trioctanoin) 7360-38-5	Triethylhexanoin is the triester of glycerin and 2-ethylhexanoic acid. It conforms generally to the formula: 	fragrance ingredient; hair conditioning agent; skin conditioning agent – occlusive
Triisononanoin 206354-95-2 56554-53-1	Triisononanoin is the triester of glycerin and a branched chain nonanoic acid. It conforms generally to the formula:  one example of an “iso”	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Triisopalmitin 68957-79-9	Triisopalmitin is the triester of glycerin and a 16 carbon branched chain aliphatic acid. It conforms to the formula:  one example of an “iso”	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Triisostearin 26942-95-0	Triisostearin is the triester of glycerin and isostearic acid. [It conforms to the structure:]  one example of an “iso”	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Triheptylundecanoin 105214-66-2	Triheptylundecanoin is the triester of glycerin and heptylundecanoic acid. It conforms to the formula: 	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous

Table 2. **Definitions, idealized structures, and functions of the ingredients in this safety assessment.** [7;[CIR Staff]]

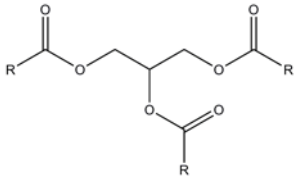
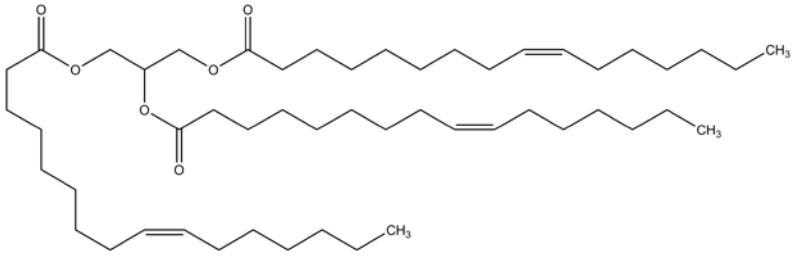
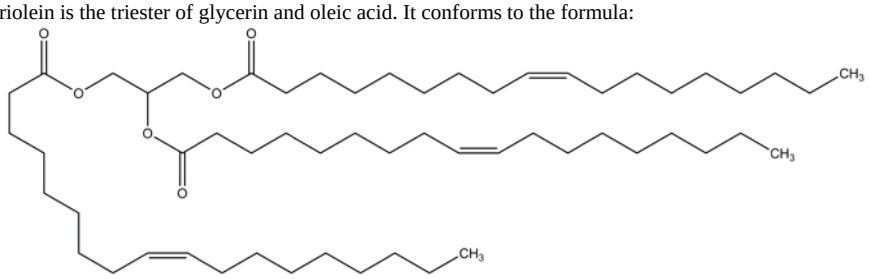
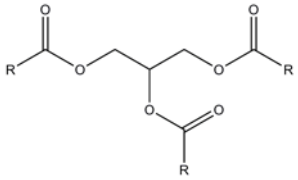
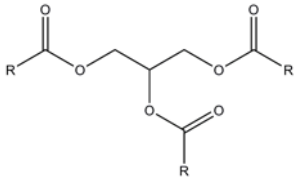
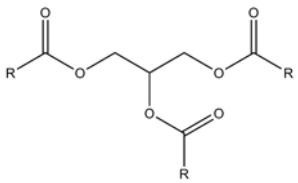
Ingredient/CAS No.	Definition & Structure	Function(s)
	Branched, mixed length chain triglyceride	
C10-40 Isoalkyl Acid Triglyceride	C10-40 Isoalkyl Acid Triglyceride is the triester of glycerin and C10-40 Isoalkyl Acid.  [wherein RC(O)- is the residue of a branched fatty acid 10 to 40 carbons in length]	hair conditioning agent; skin conditioning agent – emollient; viscosity increasing agent - nonaqueous
	Unsaturated chain & hydroxy acid triglycerides	
Tripalmitolein 129784-33-4 20246-55-3	Tripalmitolein is the triester of glycerin and palmitoleic acid. It conforms to the formula: 	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Triolein 122-32-7 6915-08-8	Triolein is the triester of glycerin and oleic acid. It conforms to the formula: 	skin protectant; skin conditioning agent – emollient, occlusive, misc; viscosity increasing agent - nonaqueous
Oleic/Linoleic Triglyceride	Oleic/Linoleic Triglyceride is the mixed triester of glycerin with oleic and linoleic acids.  [wherein RC(O)- is the residue of oleic or linoleic acid]	skin conditioning agent – occlusive
Docosahexenoic/ Docosapentenoic/ Oleic/Palmitic Triglyceride	Docosahexenoic/Docosapentenoic/Oleic/Palmitic Triglyceride is the mixed triester of glycerin with docosahexenoic, docosapentenoic, oleic, and palmitic acids.  [wherein RC(O)- is the residue of docosahexenoic, docosapentenoic, oleic, or palmitic acid.]	skin bleaching agent; skin protectant; skin conditioning agent – misc
Isomerized Safflower Glycerides 303101-61-3	Isomerized Safflower Glycerides is the product formed by the esterification of glycerin and isomerized safflower acid.  [wherein RC(O)- is the residue of a fatty acid derived from safflower oil, which is approximately 68% linoleic, 25% oleic, and 2% palmitic][50]	oral health care drug; skin conditioning agent - misc

Table 2. Definitions, idealized structures, and functions of the ingredients in this safety assessment. [7;[CIR Staff]]

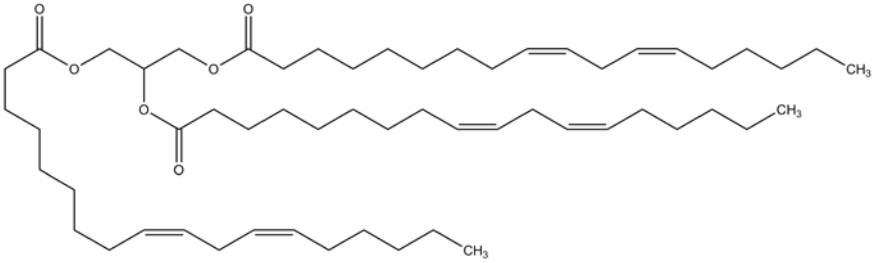
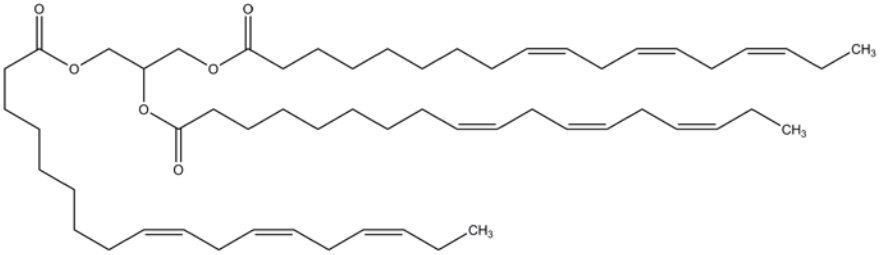
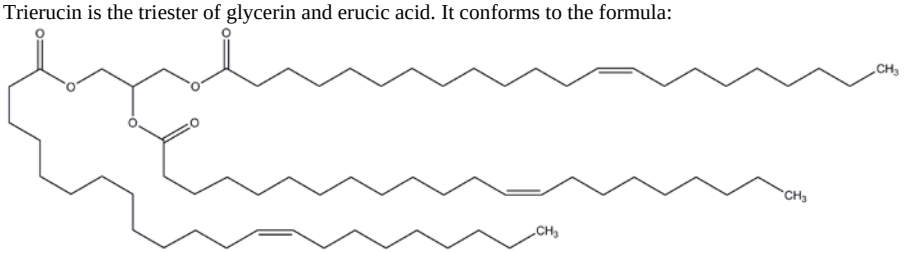
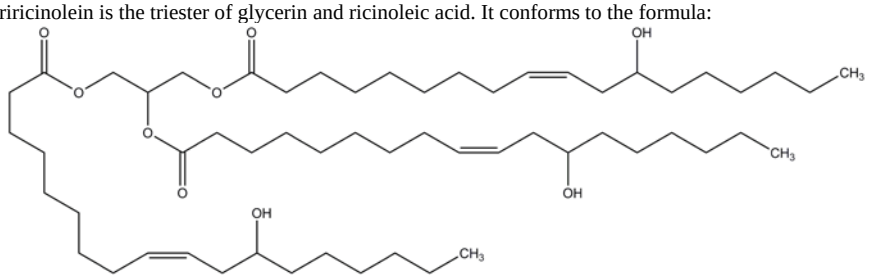
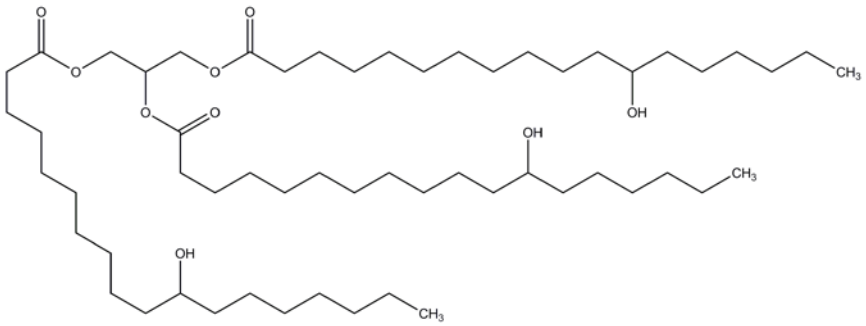
Ingredient/CAS No.	Definition & Structure	Function(s)
Trilinolein 537-40-6	Trilinolein is the triester of glycerin and linoleic acid. It conforms to the formula: 	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Trilinolenin 14465-68-0	Trilinolenin is the triester of glycerin and linolenic acid. It conforms to the formula: 	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Trierucin 2752-99-0	Trierucin is the triester of glycerin and erucic acid. It conforms to the formula: 	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Triricinolein 15505-14-3 2540-54-7	Triricinolein is the triester of glycerin and ricinoleic acid. It conforms to the formula: 	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Trihydroxystearin 139-44-6	Trihydroxystearin is the triester of glycerin and hydroxystearic acid. It conforms generally to the formula: 	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous

Table 2. **Definitions, idealized structures, and functions of the ingredients in this safety assessment.** [7;[CIR Staff]]

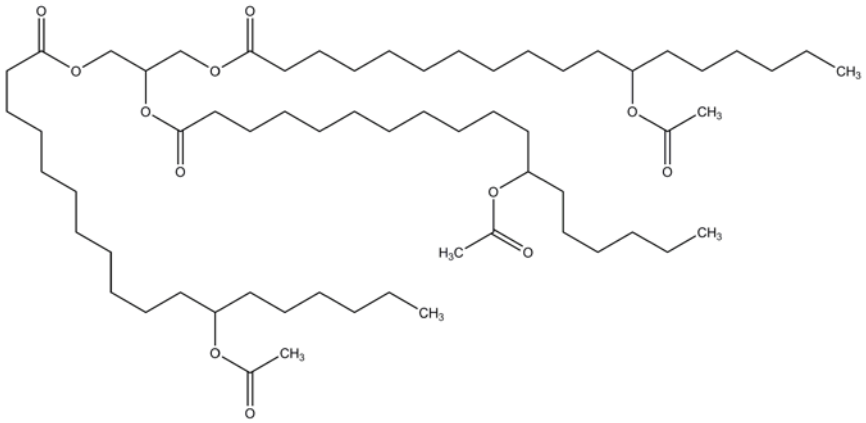
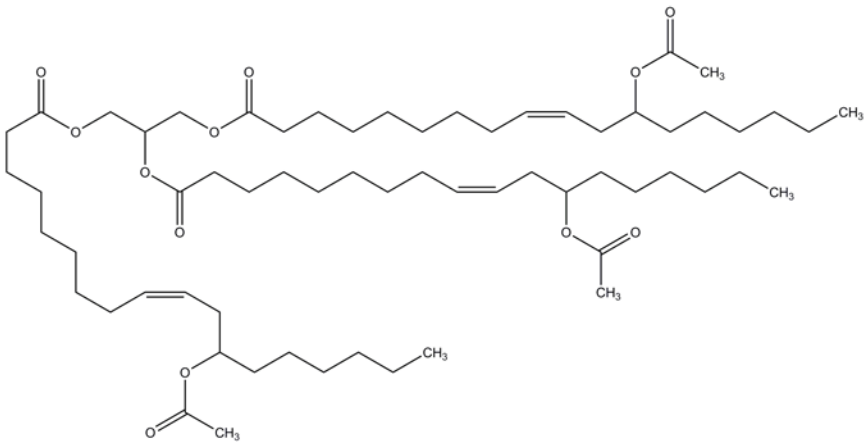
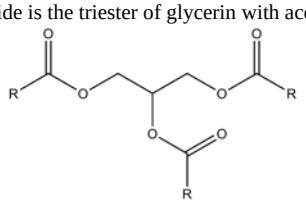
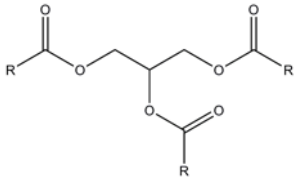
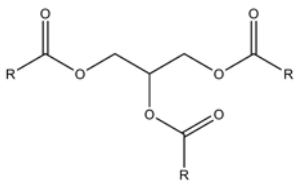
Ingredient/CAS No.	Definition & Structure	Function(s)
	Acetylated hydroxyacid triglycerides	
Glyceryl Triacetyl Hydroxystearate 27233-00-7	Glyceryl Triacetyl Hydroxystearate is the triester of glycerin and acetyl hydroxystearic acid. It conforms to the formula: 	skin conditioning agent - emollient
Glyceryl Triacetyl Ricinoleate 101-34-8	Glyceryl Triacetyl Ricinoleate is the triester of glycerin and acetyl ricinoleic acid. It conforms to the formula: 	skin conditioning agent - emollient
	Mixed chain – others (combinations of length, saturation, and branching variations)	
Acetic/Linoleic/Palmitic Triglyceride 221139-79-3	Acetic/Linoleic/Palmitic Triglyceride is the triester of glycerin with acetic, linoleic and palmitic acids.  [wherein RC(O)- is the residue of acetic, linoleic, or palmitic acid.]	skin conditioning agent – emollient; skin conditioning agent - humectant
Capric/Lauric/Myristic/ Oleic Triglyceride	Capric/Lauric/Myristic/Oleic Triglyceride is the mixed triester of glycerin with caprylic, capric, lauric, myristic and oleic acids.  [wherein RC(O)- is the residue of caprylic, capric, lauric, myristic, or oleic acid.]	skin protectant; skin conditioning agent – emollient; skin conditioning agent - misc
Caprylic/Capric/Linoleic Triglyceride	Caprylic/Capric/Linoleic Triglyceride is the mixed triester of glycerin with caprylic, capric and linoleic acids.  [wherein RC(O)- is the residue of caprylic, capric, or linoleic acid.]	skin conditioning agent - occlusive

Table 2. Definitions, idealized structures, and functions of the ingredients in this safety assessment. [7;[CIR Staff]]

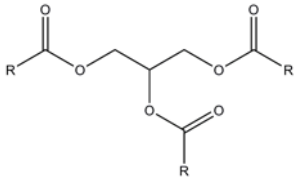
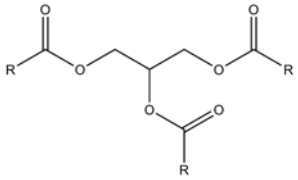
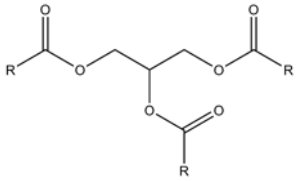
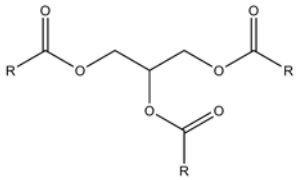
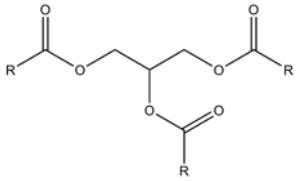
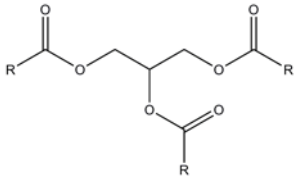
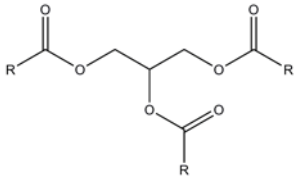
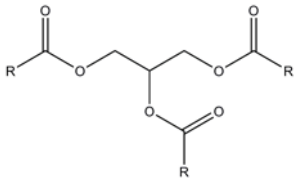
Ingredient/CAS No.	Definition & Structure	Function(s)
Cod Liver/Mink/Tallow Triglyceride	Cod Liver/Mink/Tallow Triglyceride is a mixed triester of glycerin with the fatty acids derived from cod liver oil, mink oil, and tallow  [wherein RC(O)- is the residue of a fatty acid derived from cod liver oil (which is approximately 16.2% oleic acid, 11.9% docosahexaenoic acid, 10.4% palmitic acid, 9.4% gondoic acid (20:1 *n*-9), 9.3% eicosapentaenoic acid, 7.8% cetoleic acid (22:1 n-11), 6.5% palmitoleic acid, 4.4% cis-vaccenic acid, 3.6% myristic acid, 2.6% stearic acid, 2.4% moroctic acid, 1.6% gadoleic acid (20:1 *n*-11), 1.5% linoleic acid,)[51], mink oil (which is approximately 35-41% oleic acid, 17-28% palmitic acid (16/0), 13-17% palmitic acid (16/1), and 11-15% linoleic acid),[52] and tallow (which is approximately 37-43% oleic acid, 24-32% palmitic acid, 20-25% stearic acid, 3-6% myristic acid, and 2-3% linoleic acid)[53]].	skin conditioning agent – emollient; skin conditioning agent - occlusive
Glyceryl Tri-Hydrogenated Rosinate	Glyceryl Tri-Hydrogenated Rosinate is a triester of glycerin and the partially hydrogenated acids derived from Rosin  [wherein RC(O)- is the residue of the partially hydrogenated acids derived from rosin.].	surfactant – emulsifying agent
Glyceryl Tripalmate/ Palm Kernelate/Olivate/ Macadamiate/ Rapeseedate	Glyceryl Tripalmate/Palm Kernelate/Olivate/Macadamiate/Rapeseedate is the triester of glycerin with a mixture of fatty acids derived from palm oil, palm kernel oil, olive oil, macadamia nut oil and rapeseed oil.  [wherein RC(O)- is the residue of a fatty acid derived from palm oil (which is approximately 44% palmitic acid, 39% oleic acid, and 10% linoleic acid), palm kernel oil (which is approximately 48% lauric acid, 16% myristic acid, and 15% oleic acid), olive oil (which is approximately 53-86% oleic acid and 7.5-20% palmitic acid,), macadamia oil (which is approximately 50-67% oleic acid, 12-25% palmitoleic acid, and 6-12% palmitic acid), and rapeseed oil (which is approximately 1-59% behenic acid, 12-57% oleic acid, 11-22% linoleic acid, and 8-12.5% linolenic acid)][50]	skin conditioning agent – emollient
Hydrogenated C12-18 Triglycerides	Hydrogenated C12-18 Triglycerides is the end-product of controlled hydrogenation of C12-18 triglycerides.  [wherein RC(O)- is the residue of hydrogenated of C12-18 acids]	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Jojoba Oil/Caprylic/Capric Triglyceride Esters	Jojoba Oil/Caprylic/Capric Triglyceride Esters is the product obtained by the transesterification of Simmondsia Chinensis (Jojoba) Seed Oil with Caprylic/Capric Triglyceride.  [wherein RC(O)- is the residue of caprylic acid, capric acid, and a fatty acid derived from jojoba, which is approximately 83%as combinations of arachidic and behenic acids[54]]	skin protectant; skin conditioning agent – emollient

Table 2. Definitions, idealized structures, and functions of the ingredients in this safety assessment. [7;[CIR Staff]]

Ingredient/CAS No.	Definition & Structure	Function(s)
Lauric/Palmitic/Oleic Triglyceride	Lauric/Palmitic/Oleic Triglyceride is a mixed triester of glycerin with lauric, palmitic and oleic acids.  [wherein RC(O)- is the residue of lauric, palmitic, or oleic acid]	skin conditioning agent – occlusive
Oleic/Palmitic/Lauric/ Myristic/Linoleic Triglyceride	Oleic/Palmitic/Lauric/Myristic/Linoleic Triglyceride is the mixed triester of glycerin with oleic, palmitic, lauric, myristic and linoleic acids.  [wherein RC(O)- is the residue of oleic, palmitic, lauric, myristic, or linoleic acid]	skin conditioning agent – occlusive
Ricinoleic/Caproic/ Caprylic/Capric Triglyceride	Ricinoleic/Caproic/Caprylic/Capric Triglyceride is the mixed triester of glycerin with ricinoleic, caproic, caprylic and capric acids.  [wherein RC(O)- is the residue of ricinoleic, caproic, caprylic, or capric acid]	skin conditioning agent – occlusive

Note: ingredients that were previously reviewed are indicated in blue

Table 3. Previously Reviewed Components and Related Glyceryl Esters

Component	Conclusion	Reference
Glycerin	safe in cosmetics in the present practices of use and concentration	8
Monoglyceryl Monoesters, including Glyceryl Acetate, Glyceryl Arachidate, Glyceryl Behenate, Glyceryl Caprate, Glyceryl Caprylate, Glyceryl Caprylate/ Caprate, Glyceryl Citrate/Lactate/Linoleate/Oleate, Glyceryl Cocoate, Glyceryl Erucate, Glyceryl Ethylhexanoate, Glyceryl Heptanoate, Glyceryl Hydrogenated Rapeseedate, Glyceryl Hydrogenated Rosinate, Glyceryl Hydrogenated Soyate, Glyceryl Hydroxy-stearate, Glyceryl Isopalmitate, Glyceryl Isostearate, Glyceryl Isotridecanoate/Stearate/ Adipate, Glyceryl Laurate, Glyceryl Laurate SE, Glyceryl Laurate/ Oleate, Glyceryl Linoleate, Glyceryl Linolenate, Glyceryl Oleate, Glyceryl Oleate SE, Glyceryl Oleate/Elaidate, Glyceryl Olivate, Glyceryl Palmitate, Glyceryl Palmitate/Stearate, Glyceryl Palmitoleate, Glyceryl Ricinoleate, Glyceryl Ricinoleate SE, Glyceryl Rosinate, Gly-ceryl Stearate , Glyceryl Stearate SE, Glyceryl Stearate/Malate, Glyceryl Tallowate, Glyceryl Undecylenate	safe in the present practices of use and concentration	2
Diglycerides, includes: Glyceryl Dilaurate, Glyceryl Diarachidate, Glyceryl Dibehenate, Glyceryl Dierucate, Glyceryl Dihydroxystearate, Glyceryl Diisopalmitate, Glyceryl Diisostearate, Glyceryl Dilinoleate, Glyceryl Dimyristate, Glyceryl Dioleate, Glyceryl Diricinoleate, Glyceryl Dipalmitate, Glyceryl Dipalmitoleate, Glyceryl Distearate	safe in the present practices of use and concentration, provided the content of 1,2-diesters is not high enough to induce epidermal hyperplasia	9
Acetic Acid	safe in the present practices of use and concentration	55
Caprylic/Capric/Coco Glycerides	safe for use as a cosmetic ingredient	56
Carthamus Tinctorius (Safflower) Seed Oil	safe in the present practices of use and concentration	50
Coconut Acid; Cocos Nucifera (Coconut) Oil	safe for use as a cosmetic ingredient	50
Cocoglycerides; Hydrogenated Coco-Glycerides	safe for use as a cosmetic ingredient	56
Elaeis Guineensis (Palm) Oil; Elaeis Guineensis (Palm) Kernel Oil	safe in the present practices of use and concentration	50
Hydroxystearic Acid	safe as a cosmetic ingredient in the present practices of use	57
Isostearic Acid	safe as a cosmetic ingredient in the present practices of use	57
Lauric Acid	safe in the present practices of use and concentration	58
Macadamia Nut Oil	safe in the present practices of use and concentration	50
Mink Oil	safe in the present practices of use and concentration	52
Myristic Acid Glyceryl Dimyristate Glyceryl Isostearate/Dimyristate	safe in the present practices of use and concentration	59
Oleic Acid	safe in the present practices of use and concentration	58
Olive Acid; Olea Europaea (Olive) Fruit Oil	safe in the present practices of use and concentration	50
Palmitic Acid	safe in the present practices of use and concentration	58
Pelargonic Acid	safe in the present practices of use and concentration	60
Rapeseed Acid; Hydrogenated Rapeseed Oil	safe in the present practices of use and concentration	50
Ricinoleic Acid; Ricinus Communis (Castor) Seed Oil; Hydrogenated Castor Oil	safe in the present practices of use and concentration	61
Shea Oleine	safe in cosmetics in the present practices of use and concentration when formulated to be non-sensitizing	62
Simmondsia Chinensis (Jojoba) Seed Oil	safe in the present practices of use and concentration	63
Soy Acid; Hydrogenated Soybean Oil	safe in the present practices of use and concentration	50
Stearic Acid	safe in the present practices of use and concentration	58
Tallow; Tallow Glyceride; Hydrogenated Tallow Glyceride; Tallow Glycerides; Hydrogenated Tallow Glycerides	safe as a cosmetic ingredient in the present practices of use	53

Table 4. Physical and Chemical Properties

	form	molecular weight	melting point (°C)	specific gravity	density	solubility	refractive index	o/w partition coefficient	saponification value	acid value	hydroxyl value
Triheptanoin[31]	liquid	428.6	-25		0.964 (at 20°C)	water solubility - <0.05 mg/l		8.86			
Tricaprylin[4]		470.70	10 (stable); -22 (unstable)		0.9540 (at 20°C)	soluble in ethanol, diethyl ether, benzene, chloroform, and ligroin	1.4482 (at 20°C)				
Tripelargonin[64]		512.76			0.959 (at 20°C)			10.915			
Triundecanoin[4]	colorless to slightly amber liquid or white to off-white, waxy solid					Soluble in petroleum ether, chloroform, and hot alcohol; insoluble in water			265-290	10 max	25 max
Trilaurin[4]	needles (obtained from alcohol as solvent)	638.97	36		0.8986 (at 55°C)	insoluble in water; soluble in alcohol, ether, chloroform, and petroleum either; very soluble in acetone and benzene	1.4404 (at 60°C)		261		
Trimyristin[4]	polymorphic (crystallized from ethanol and diethyl ether)	768.28	56.5 (stable) 32 (unstable)			soluble in ether, acetone, benzene, and chloroform	1.4428 (at 60°C)				
Tripalmitin[4]	needles (obtained from ethanol as solvent)	807.35	66 (stable) 44.7 (unstable)		0.8752 (at 70°C)	soluble in ether, benzene, and chloroform	1.4381 (at 80°C)				
Tristearin[4]		891.51			0.8559 (at 90°C)	soluble in acetone	1.4395 (at 80°C)				
Caprylic/Capric Triglyceride[5]				0.92-0.96 (25°C/25°C)		soluble in ethanol to ~20% by weight	1.4480-1.4510	>3[35]	300-360	0.1 max	5.0 max
Triethylhexanoin[25]	colorless to pale yellow, transparent oily liquid	470	73.03 (estimated)			water solubility – 1.2 x 10^{-7} g/l (at 20°C; calculated)		>6.5[35] 8.98 (calc)			
Triisostearin[4]	Light yellow, oily substance								185-210	3 max	30 max
Triolein[4]	Colorless to yellowish oily liquid polymorphic	885.47	-32[35]		0.8988 (at 60°C)	Practically insoluble in water; slightly soluble in alcohol; soluble in chloro-form, ether, petroleum ether, and carbon tetrachloride	1.4621 (at 40°C)		192-202	5 max	10 max
Trihydroxystearin[1]	white, finely divided powder	939.49	85-86	1.023 (at 25°C)	8.51						

Table 5. 2017[13-15] and historical[1,4-6] frequency and concentration of use of triglycerides according to duration and exposure

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	Caprylic/Capric Triglyceride				Glyceryl Triacetyl Hydroxystearate			
	2017	2003	2017	2003[6]	2017	1998	2017	1998
Totals*	**6000**	**763**	**0.0000067-95.6**	**0.00001-84**	**20**	**3**	**1-19.6**	**9**
Leave-On	*5403*	*704*	*0.0000067-95.6*	*0.00001-84*	*20*	*3*	*1-19.6*	*9*
Rinse-Off	*574*	*59*	*0.0000067-89.2*	*0.002-10*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*23*	*NR*	*0.099*	*7-78*	*NR*	*NR*	*NR*	*NR*
Eye Area	1063	207	1-83.3	0.008-49	NR	NR	NR	NR
Incidental Ingestion	585	75	1.2-54	0.002-54	20	2	1-19.6	9
Incidental Inhalation-Spray	122; 1446[a]; 1356[b]	30; 150[a]; 104[b]	0.019-38.6; 0.00001-28.8[a]; 0.0034-1.3[b]	0.00005-84; 0.0001-19[a]; 0.06-48[b]	NR	1[a]	NR	NR
Incidental Inhalation-Powder	77; 1356[b]; 25[c]	11; 104[b]; 2[c]	3.2-16; 0.0034-1.3[b]; 0.67-95.6[c]	0.01-22; 0.06-48[b]; 0.8[c]	NR	NR	NR	NR
Dermal Contact	5195	672	0.000021-95.6	0.00005-84	NR	NR	NR	NR
Deodorant (underarm)	6[b]	1[b]	not spray: 0.000021-9; spray: 0.09-0.99	0.00005-5[b]	NR	NR	NR	NR
Hair - Non-Coloring	161	10	0.0000067-89.2	0.00005-18	NR	1	NR	NR
Hair-Coloring	22	1	0.00002-4.1	NR	NR	NR	NR	NR
Nail	17	5	0.08-50	0.2-15	NR	NR	1-19.6	NR
Mucous Membrane	698	75	0.0001-55.7	0.002-78	20	2	NR	9
Baby Products	37	5	3.2-52	0.8	NR	NR	NR	NR
	Glyceryl Triacetyl Ricinoleate				Tribehenin			
	2017	1998	2017	1998	2017	1998	2017	1998
Totals*	**17**	**32**	**1-49.2**	**8**	**723**	**42**	**0.002-15**	**0.31-6**
Duration of Use								
Leave-On	*17*	*32*	*1-49.2*	*8*	*695*	*38*	*0.002-15*	*0.31-6*
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*28*	*4*	*0.002-7*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	3	NR	27.1-49.2	NR	95	3	0.04-15	0.32
Incidental Ingestion	7	31	1-8	8	249	NR	0.01-5.6	0.38
Incidental Inhalation-Spray	1[a]	NR	NR	NR	9; 77[a]; 53[b]	4[a]; 3[b]	0.002-8[a]	3[a]; 0.38[b]
Incidental Inhalation-Powder	NR	NR	6.3	NR	2; 53[b]; 1[c]	3[b]	0.015-5.4; 0.002-4.8[c]	0.38[b]
Dermal Contact	10	1	6.3.-49.2	NR	409	38	0.002-8	0.32-6
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	5.1	3-6[b]
Hair - Non-Coloring	NR	NR	NR	NR	28	4	0.015-8	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	4	NR	NR	NR
Mucous Membrane	7	31	1-8	8	255	NR	0.01-7	0.38
Baby Products	NR	NR	NR	NR	1	NR	NR	NR
	Tricaprin[d]				Tricaprylin			
	2017	1998	2017	1998	2017		1998	2017	1998
Totals*	**51**	**NR**	**0.75**	**NR**	**262**	**47[e]**	**70**	**0.0002-12.7**	**0.5-10**
Leave-On	*47*	*NR*	*0.75*	*NR*	*256*	*47*	*66*	*0.0002-11*	*0.5-10*
Rinse-Off	*4*	*NR*	*0.75*	*NR*	*6*	*NR*	*4*	*0.25-12.7*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Eye Area	5	NR	NR	NR	111	3	5	2-8	NR
Incidental Ingestion	3	NR	NR	NR	37	11	15	0.035-5	NR
Incidental Inhalation-Spray	6[a]; 17[b]	NR	NR	NR	1; 23[a]; 23[b]	9[a]; 23[b]	10[a]; 6[b]	4.1; 7[a]	2[a]; 2[b]
Incidental Inhalation-Powder	17[B]	NR	0.75[c]	NR	39; 23[a]; 1[c]	23[b]	2; 6[b]	1.5-2.3; 0.0002-7.5[c]	5; 2[b]
Dermal Contact	47	NR	0.75	NR	221	34	51	0.0002-11	0.5-10
Deodorant (underarm)	NR	NR	NR	NR	NR		NR	NR	NR
Hair - Non-Coloring	1	NR	NR	NR	4	NR	3	0.25-7	NR
Hair-Coloring	NR	NR	0.75	NR	NR	2	NR	12.7	NR
Nail	NR	NR	NR	NR	NR	NR	1	NR	NR
Mucous Membrane	3	NR	NR	NR	37	11	15	0.035-5	NR
Baby Products	NR	NR	NR	NR	1	NR	NR	NR	NR

Table 5. 2017[13-15] and historical[1,4-6] frequency and concentration of use of triglycerides according to duration and exposure

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Triethylhexanoin (previously Trioctanoin)				**Triheptanoin**			
	2017	**1998**	**2017**	**1998**	**2017**	**1998**	**2017**	**1998**
Totals*	**601**	**27**	**0.002-100**	**0.1-50**	**26**	**NR**	**4-5.3**	**12-15**
Leave-On	*574*	*25*	*0.002-100*	*0.2-46*	*22*	*NR*	*4-5.3*	*12*
Rinse-Off	*27*	*2*	*0.1-61.1*	*0.1-50*	*4*	*NR*	*NR*	*15*
Diluted for (Bath) Use	*NR*	*NR*	*52.8*	*NR*	*NR*	*NR*	*NR*	*NR*
Eye Area	131	3	0.002-52	2-17	NR	NR	4.5	NR
Incidental Ingestion	116	6	8-63	46	2	NR	5.3	12
Incidental Inhalation-Spray	11[a]; 133[b]	4[a];3[b]	0.035-36; 5[a]	1-8[a]; 3-6[b]	13[a]; 6[b]	NR	NR	NR
Incidental Inhalation-Powder	26; 133[b]	3[b]	0.83-14.7; 0.6-100[c]	3-6[b]	6[b]	NR	4-5[c]	NR
Dermal Contact	481	20	0.002-100	0.1-50	24	NR	4-5	15
Deodorant (underarm)	1[b]	NR	0.8-9	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	NR	0.035-30	0.2--1	NR	NR	NR	NR
Hair-Coloring	NR	NR	10	NR	NR	NR	NR	NR
Nail	1	NR	8-46	3	NR	NR	NR	NR
Mucous Membrane	117	6	8-63	46	3	NR	5.3	12
Baby Products	1	NR	NR	NR	NR	NR	NR	NR
	Trihydroxystearin				**Triisononanoin**			
	2017	**1997**	**2017**	**1997**	**2017**	**1998**	**2017**	**1998**
Totals*	**273**	**41**	**0.01-14.7**	**0.5-5[#]**	**15**	**8**	**1-25.3**	**25**
Leave-On	*238*	*38*	*0.01-14.7*	*NR*	*11*	*8*	*1-25.3*	*25*
Rinse-Off	*35*	*3*	*0.25-6.6*	*NR*	*4*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Eye Area	80	10	0.3-14.7	NR	NR	NR	NR	NR
Incidental Ingestion	64	6	0.5-8	NR	1	NR	25.3	25
Incidental Inhalation-Spray	11[a]; 8[b]	4[a]; 1[b]	1.5-4[a]	NR	4[a]; 4[b]	1[a]; 6[b]	NR	NR
Incidental Inhalation-Powder	2; 8[b]	4; 1[b]	1-2; 1.7-4[c]	NR	4[b]	6[b]	1-10[c]	NR
Dermal Contact	154	30	0.01-14.7	NR	14	8	1-10	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	24	NR	0.25-4	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	1	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	74	6	0.5-8	NR	5	NR	25.3	25
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
	Triisostearin				**Trilaurin**			
	2017	**1998**	**2017**	**1998**	**2017**	**1998**	**2017**	**1998**
Totals*	**291**	**5**	**0.05-45**	**36**	**125**	**197**	**0.00005-46.3**	**0.003-46**
Leave-On	*290*	*5*	*0.3-45*	*36*	*123*	*195*	*0.00005-46.3*	*0.003-46*
Rinse-Off	*1*	*NR*	*0.05-30*	*NR*	*2*	*2*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*1*
Eye Area	27	1	2-35	NR	107	145	0.2-36.3	0.003-46
Incidental Ingestion	161	4	8.3-45	36	1	14	46.3	0.2-46
Incidental Inhalation-Spray	5[a]; 10[b]	NR	6-30	NR	1; 3[a]; 3[b]	1; 2[a]; 4[b]	NR	0.96-3[a]; 0.4-3[b]
Incidental Inhalation-Powder	12; 10[b]	NR	3-10.4; 2.5-11[c]	NR	3[b]	4[b]	0.00005[c]	0.4-3[b]
Dermal Contact	130	1	0.05-35	NR	124	183	0.00005-36.3	0.003-46
Deodorant (underarm)	NR	NR	NR	NR	5[b]	NR	NR	NR
Hair - Non-Coloring	NR	NR	1-6	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	0.05-3	NR	NR	NR	NR	NR
Nail	NR	NR	45	NR	NR	NR	NR	NR
Mucous Membrane	160	4	0.8-45	36	2	14	46.3	0.2-46
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 5. 2017[13-15] and historical[1,4-6] frequency and concentration of use of triglycerides according to duration and exposure

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Trilinolein				**Trimyristin**			
	2017	**1998**	**2017**	**1998**	**2017**	**1998**	**2017**	**1998**
Totals*	**27**	**2**	**0.00048-0.017**	**NR**	**27**	**10**	**0.12-8**	**1-2**
Leave-On	*12*	*2*	*0.0048-0.017*	*NR*	*27*	*10*	*0.12-8*	*1-2*
Rinse-Off	*15*	*NR*	*0.00048-0.0048*	*NR*	*NR*	*NR*	*2*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*0.00048*	*NR*	*NR*	*NR*	*NR*	*NR*
Eye Area	NR	NR	NR	NR	3	1	0.2-8	2
Incidental Ingestion	NR	NR	0.0048	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	4[a]; 1[b]	1[a]	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	1[b]	NR	0.0048-0.017[c]	NR	10	5	0.5[c]	1
Dermal Contact	27	2	0.00048-0.017	NR	27	10	0.12	1-2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	0.12-8	NR
Hair - Non-Coloring	NR	NR	0.00048	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	15	NR	0.00048-0.0048	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
	Triolein				**Tripalmitin**			
	2017	**1998**	**2015**	**1998**	**2017**	**1998**	**2015**	**1998**
Totals*	**107**	**NR**	**0.00053-0.14**	**NR**	**12**	**1**	**0.094-19.3**	**2**
Leave-On	*92*	*NR*	*0.0008-0.14*	*NR*	*10*	*NR*	*0.094-19.3*	*NR*
Rinse-Off	*15*	*NR*	*0.00053-0.025*	*NR*	*2*	*1*	*1*	*2*
Diluted for (Bath) Use	*NR*	*NR*	*0.00053*	*NR*	*NR*	*NR*	*NR*	*NR*
Eye Area	3	NR	0.005-14	NR	8	NR	0.094-19.3	NR
Incidental Ingestion	68	NR	0.0008-0.0053	NR	NR	NR	15.6	NR
Incidental Inhalation-Spray	3[a]; 1[b]	NR	NR	NR	1[b]	NR	NR	NR
Incidental Inhalation-Powder	1[b]	NR	0.0053-0.025[c]	NR	NR	NR	0.7[c]	NR
Dermal Contact	39	NR	0.00053-0.14	NR	12	1	0.094-19.3	2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	0.00053	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	1	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	83	NR	0.00053-0.0053	NR	1	NR	15.6	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
	Tristearin				**Triundecanoin[f]**			
	2017	**1998**	**2015**	**1998**	**2017**	**1998**	**2015**	**1998**
Totals*	**66**	**46**	**0.004-24**	**3**	**4**	**NR**	**1.5**	**NR**
Leave-On	*54*	*42*	*0.004-24*	*3*	*3*	*NR*	*NR*	*NR*
Rinse-Off	*12*	*4*	*NR*	*NR*	*1*	*NR*	*1.5*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Eye Area	9	22	0.004-24	2	NR	NR	NR	NR
Incidental Ingestion	3	4	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	2; 14[a]; 14[b]	2; 3[a]; 5[b]	NR	NR	2[a]; 1[b]	NR	NR	NR
Incidental Inhalation-Powder	14[b]	5[b]	NR	NR	1[b]	NR	NR	NR
Dermal Contact	63	42	0.004-24	0.1-3	4	NR	1.5	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	12	4	NR	NR	NR	NR	1.5	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
**at the time of the original safety assessment, concentration of use data were not reported by the FDA.
[#] a concentration range was specified, but not details were provided
[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays..
[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders
[d] as Capric Triglyceride in VCRP
[e] as Caprylic Triglyceride in VCRP
[f] as Glyceryl Triundecanoate in VCRP
NR – no reported use

Table 6. Frequency[13] and concentration of use[14,15] previously unreviewed triglycerides

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	C12-18 Acid Triglyceride		**C18-36 Acid Triglyceride**		**Caprylic/Capric/Lauric Triglyceride**	
Totals*	**18**	**0.2-0.33**	**216**	**0.64-26.1**	**4**	**NR**
Duration of Use						
Leave-On	*18*	*0.2-0.33*	*216*	*0.64-26.1*	4	*NR*
Rinse-Off	*NR*	*NR*	*NR*	*NR*	NR	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	NR	*NR*
Exposure Type						
Eye Area	2	0.2-0.33	92	0.76-4.5	NR	NR
Incidental Ingestion	14	NR	NR	1.3-26.1	NR	NR
Incidental Inhalation-Spray	1[a]	NR	3; 1[a]; 5[b];	9.2; 11[a]	2[a]; 2[b]	NR
Incidental Inhalation-Powder	1; 1[a]	NR	1[a]	NR	2[a]	NR
Dermal Contact	4	0.2-0.33	134	0.64-20	3	NR
Deodorant (underarm)	NR	NR	NR	0.64-3.5	NR	NR
Hair - Non-Coloring	NR	NR	3	11	1	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	1	NR	NR	NR
Mucous Membrane	14	NR	NR	1.3-26.1	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Caprylic/Capric/Linoleic Triglyceride		**Caprylic/Capric/Myristic/Stearic Triglyceride**		**Caprylic/Capric/Stearic Triglyceride**	
Totals*	**NR**	**0.001-52.1**	**229**	**0.015-15.3**	**22**	**1-17.7**
Duration of Use						
Leave-On	*NR*	*0.001-52.1*	217	*0.015-15.3*	21	*1-17.7*
Rinse Off	*NR*	*NR*	12	*0.1-8*	1	*2*
Diluted for (Bath) Use	*NR*	*NR*	NR	*NR*	NR	*NR*
Exposure Type						
Eye Area	NR	NR	29	0.075-15.3	3	1.3-17.7
Incidental Ingestion	NR	NR	7	1.9-8.6	1	NR
Incidental Inhalation-Spray	NR	NR	1; 156[a]; 18[b]	0.1-6[a]	6; 7[a]; 2[b]	NR
Incidental Inhalation-Powder	NR	0.001-52.1[c]	156[a]	0.18-8[c]	7[a]	1[C]
Dermal Contact	NR	0.001-52.1	221	0.015-15.3	18	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	1	0.1-5	3	2
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	12	1.9-8.6	2	NR
Baby Products	NR	NR	NR	NR	NR	NR

	C10-40 Isoalkyl Acid Triglyceride		**C10-18 Triglycerides**		**Glyceryl Tri-Hydrogenated Rosinate**	
Totals*	**1**	**NR**	**93**	**0.0049-48.4**	**NR**	**61**
Duration of Use						
Leave-On	*1*	*NR*	*91*	*0.0049-48.4*	*NR*	*NR*
Rinse-Off	*NR*	*NR*	*1*	*0.0049-0.25*	*NR*	*61*
Diluted for (Bath) Use	*NR*	*NR*	*1*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	23	3.5-43.9	NR	NR
Incidental Ingestion	1	NR	11	0.1-48.4	NR	NR
Incidental Inhalation-Spray	NR	NR	22[a]; 22[b]	1.3[a]	NR	NR
Incidental Inhalation-Powder	NR	NR	1; 22[a]; 1[c]	0.1-2.7; 0.0049-5[c]	NR	NR
Dermal Contact	NR	NR	82	0.0049-43.9	NR	61
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	0.25	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	NR	12	0.1-48.4	NR	NR
Baby Products	NR	NR	1	NR	NR	NR

Table 6. Frequency[13] and concentration of use[14,15] previously unreviewed triglycerides

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Hydrogenated C12-18 Triglycerides		**Palmitic/Stearic Triglyceride**		**Trilinolenin[d]**	
Totals*	**12**	**1-39.3**	**6**	**NR**	**2**	**NR**
Duration of Use						
Leave-On	*10*	*1-39.3*	*6*	*NR*	*2*	*NR*
Rinse-Off	*2*	*NR*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	39.3	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	1[a]; 5[b]	NR	2[a]; 3[b]	NR	2[a]	NR
Incidental Inhalation-Powder	1[a]	NR	2[a]; 1[c]	NR	2[a]	NR
Dermal Contact	12	1-39.3	6	NR	2	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	NR	NR	NR	NR	NR
Baby Products	NR	NR	1	NR	NR	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[a] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories
[b] It is possible these products are sprays, but it is not specified whether the reported uses are sprays..
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders
[d] as Linoleic Acid Triglyceride in VCRP
NR – no reported use

Table 7. Ingredients not reported to be in use[13-15]

Acetic/Linoleic/Palmitic Triglyceride	Glyceryl Tripalmate/Palm Kernelate/Olivate/Macadamiate/Rapeseedate	Triarachidin
C8-12 Acid Triglyceride	Isomerized Safflower Glycerides	Trierucin
Capric/Lauric/Myristic/Oleic Triglyceride	Jojoba Oil/Caprylic/Capric Triglyceride Esters	Triheptylundecanoin
Caprylic/Capric/Palmitic/Stearic Triglyceride	Lauric/Palmitic/Oleic Triglyceride	Triisopalmitin
Cod Liver/Mink/Tallow Triglyceride	Oleic/Linoleic Triglyceride	Tripalmitolein
Docosahexenoic/Docosapentenoic/Oleic/Palmitic Triglyceride	Oleic/Palmitic/Lauric/Myristic/Linoleic Triglyceride	Tripelargonin
Glyceryl Stearate Diacetate	Ricinoleic/Caproic/Caprylic/Capric Triglyceride	Triricinolein

Table 8. Acute Toxicity Studies

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Procedure	LD_{50}/observations	Reference
			DERMAL			
Triheptanoin	rats	5/sex	none	24 h semi-occlusive patch with 2 g/kg	>2 g/kg	31
Tristearin	rats	5/sex	corn oil	24 h semi-occlusive patch with 2 g/kg	>2 g/kg	32
			ORAL			
Triheptanoin	NMRI mice	5 males	none	5 g/kg by gavage	>5 g/kg	31
Tripelargonin; Triethylhexanoin	newborn Rhesus (*Macaca mulatta*) monkeys	5	none	8.4 ml/kg bw by nasogastric tube	Did not affect alertness or activity level; did not induce narcolepsy	29
Triethylhexanoin	rats	not provided	not provided	not specified	>48 g/kg	35
Triisostearin	Swiss mice	5 females	none	2 g/kg by gavage	>2 g/kg	33
Triisostearin	Sprague-Dawley rats	5/sex	none	2 g/kg by gavage	>2 g/kg	33
Triolein	Wistar rats	5/sex	none	2 g/kg by gavage	>2 g/kg	34
MLCT	Wistar rats	5/sex	none	5 g/kg MLCT oil or mixed rapeseed and soybean oils (7:3; control) by gavage	>5 g/kg	28

Abbreviations: MLCT – medium- and long-chain triacylglycerol (length C8 -C24)

Table 9. Short-Term, Subchronic, and Chronic Oral Toxicity Studies

Ingredient	Animals/Group	Study Duration	Vehicle	Dose	Procedure	Results	Reference
SHORT-TERM TOXICITY STUDIES							
ANIMAL							
ORAL							
Caprylic/Capric Triglyceride, 33% (v/v)	Han-Wistar rats, 3/sex	28 days (1/sex was dosed for 32 days)	water	0 or 3.12 g/kg	animals were dosed orally (assumed by gavage), 1x/day, with a dose volume of 10 ml/kg	no clinical signs of toxicity were observed; no differences in clinical pathology parameters, cytochrome P450 induction, or gross or microscopic lesions were observed	36
Caprylic/Capric Triglyceride	Han-Wistar rats, 15/sex	28 days	none	undiluted	Animals were dosed daily by gavage (dose vol 0.5 and 2 ml/kg/day) Controls were dosed with 0.5% carboxy-methylcellulose/0.1% Tween 80 in water (2 ml/kg/day) Ten animals/sex were killed at the termination of dosing; a recovery group of 5 animals/sex were killed after a subsequent 4-wk non-treatment period	Soft and/or mucoid stools were observed in 12 male and 11 female test animals Absolute and relative thymic weights were decreased in males and females without histological alterations; histopathology revealed increased alveolar histio-cytosis with focal interstitial inflammation in lungs in 5/10 test males and 7/10 test females, compared to 1/10 male and 1/10 female controls; all effects were reversible during the recovery period Statistically significant changes noted in clinical chemistry and urinalysis parameters were reversible	37
Caprylic/Capric Triglyceride	Göttingen mini-pigs; 3/sex	6 wks	none	undiluted; 0.5 or 2 ml/kg/day	Animals were dosed daily by gavage Controls were dosed with 0.5% methyl-cellulose/0.1% Tween 80 in water (2 ml/kg/day)	0.5 and 2 ml/kg/day: transient tremors, abnormal feces color, and increased triglycerides. 2 ml/kg/day: also, reduced motor activity, decreased food intake, respiratory signs (2/6 animals) and in-creased total and LDL-cholesterol; at necropsy, the lung of 3/6 animals presented abnormal color and/or irregular surface correlated with a chronic bronchio-lo-alveolar inflammation (attributed by the research-ers to aspiration pneumonia) No changes in organ weights or gross or microscopic lesions were observed, and no toxicologically-rele-vant changes in hematology or urinalysis parameters were noted	38
Caprylic/Capric Triglyceride	Wistar rats, 10 males/group	30 days	none	10.2 – 20.1 g/kg bw/day	animals were dosed once daily by gavage, in accord with OECD TG 407	NOAEL = ~10 g/kg bw/day reduced food consumption, softened feces, ruffled fur were observed in the high dose group during the first days of the study	39
MLCT	Wistar rats; 20 males/group	6 wks	none	diet containing 7% MLCT or rapeseed oil (control) (equiv to 3.5 g/kg/day)	6-wk dietary study	NOAEL = 3.5 g/kg/day no adverse effects were observed feed consumption, total carcass protein, and serum cholesterol values were statistically significantly in-creased; total body fat was statistically significantly decreased	28
PARENTERAL							
Tripelargonin/LCT (7/3 wt/wt) emulsion	New Zealand rabbits; 8 male	11 days	none	46.5% of total daily energy	TPN infusions 7 h/day; controls were given isocaloric amounts of a standard food; the animals were killed on day 12	No signs of toxicity; no effect on organ weights or liver lipid concentrations; macroscopic, but not microscopic, changes were noted in the liver	30,40

Table 9. Short-Term, Subchronic, and Chronic Oral Toxicity Studies

Ingredient	Animals/Group	Study Duration	Vehicle	Dose	Procedure	Results	Reference
				HUMAN			
MLCT	20 healthy males and females	4 wks		"bread" containing mixed rapeseed and soybean oils (7:3; controls) or MLCT; 42 g oil/ day consumed	placebo-controlled double blind study ; hematology and urinalysis were conducted at study initiation and study termination; liver and renal function were measured; body wts and body mass index were measured	no adverse effects	[28]
				SUBCHRONIC TOXICITY STUDIES			
Caprylic/Capric Triglyceride	Wistar rats, 20/sex	90 days	none	1 and 5%	dietary study, in accord with OECD TG 408; changes in organ weights were not measured; microscopic examination was not performed	NOAEL = 5% no signs of systemic toxicity; all animals survived until study termination; no effects on body weight gain, hematology, clinical chemistry, urinalysis, or gross pathology	[39]
Caprylic/Capric Triglyceride	Beagle dogs, 4/sex	91 days	none	0, 5, 10, and 15%	3-h feeding regimen for the course of the study; dry dog food with beef tallow; animals were observed daily; body weight and feed consumption were measured; hematology, serum chemistry, and urine analysis were performed	NOAEL = 15% No toxicologically-significant clinical signs of toxicity; no significant differences in body wts or feed consumption; no mortality; no test article-related changes in hematology parameters; some changes in clinical chemistry parameters may have been related to the test article; decreased urine volume with increased specific gravity was reported in the mid- and high-dose group	[41]
				CHRONIC TOXICITY STUDIES			
oil consisting of: 64% Triheptanoin 34% diheptanoin 2% monoheptanoin	Wistar rats, 10 males	9 mos	none	control diet with either 30% or 50% substitution of soybean oil with test oil	animals were exposed to *ad* libitum; controls were fed AIN-3 diet (lipid source is exclusively soybean oil); body wts were measured; biochemistry analysis (for hepatic and renal function) was performed; the liver, kidneys, and small intestine were examined microscopically	no toxic effects were observed	[42]

Abbreviations: LCT – long chain triglyceride (length $C_{16:0}$ – $C_{18:3}$); MLCT – medium- and long-chain triacylglycerol (length C_8 - C_{24}); NOAEL – no-observable adverse effect level; OECD – Organisation for Economic Cooperation and Development; TG – test guideline; TPN – total parenteral nutrition

Table 10. Genotoxicity studies

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
IN VITRO						
Tristearin	5000 µg/plate	95% ethanol	*S. typhimurium* TA1535, TA1537, TA98, TA100	Ames test, in accord with OECD TG 471, with and without metabolic activation; solvent and appropriate positive controls were used	negative	[32]
Caprylic/Capric Triglyceride	not stated	not stated	not stated	Ames test	negative	[35]
Triethylhexanoin	50-5000 µg/plate	DMSO	*S. typhimurium* TA1535, TA1537, TA98, TA100, TA102	Ames test, in accord with OECD TG 471, with and without metabolic activation; solvent and appropriate positive controls were used	negative	[25]
Triethylhexanoin	7.5-4000 µg/ml	ethanol	human lymphocytes	mammalian chromosomal aberration assay, in accord with OECD TG 473; with and without metabolic activation; solvent and appropriate positive controls were tested	negative	[25]
Triisononanoin	50-5000 µg/plate	acetone	*S. typhimurium* TA1535, TA1537, TA98, TA100 *Escherichia coli* WP2uvrA	Ames test, with and without metabolic activation; solvent and appropriate positive controls were used	negative	[44]
Triisononanoin	10-320 µg/ml	acetone	cultured peripheral human lymphocytes	chromosomal aberration assay, with and without metabolic activation; solvent and appropriate positive controls were used	negative	[44]
Triisononanoin	5-80 µg/ml	acetone	mouse lymphoma L5178Y cells	mammalian cell gene mutation assay, with and without metabolic activation; solvent and appropriate positive controls were used	negative	[44]
lipid emulsion comprised of Caprylic/Capric Triglyceride, soybean oil, olive oil, and fish oil	not provided	not provided	*S. typhimurium*	Ames test (details not provided)	negative	[27]
lipid emulsion comprised of Caprylic/Capric Triglyceride , soybean oil, olive oil, and fish oil	not provided	not provided	human lymphocytes	chromosomal aberration assay (details not provided)	negative	[27]
lipid emulsion comprised of Caprylic/Capric Triglyceride , soybean oil, olive oil, and fish oil	not provided	not provided	V79 cells	HPRT gene mutation assay (details not provided)	negative	[27]
MLCT	313-5000 µg/plate	sodium phosphate buffer	*S. typhimurium* TA1535, TA1537, TA98, TA100 *E. coli* WP2uvrA	Ames test, with and without metabolic activation; solvent and appropriate positive controls were used	negative	[28]
IN VIVO						
lipid emulsion comprised of Caprylic/Capric Triglyceride , soybean oil, olive oil, and fish oil	not provided	not provided	rats	bone marrow cytogenic study (details not provided)	negative	[27]

Abbreviations: DMSO – dimethyl sulfoxide; HPRT - hypoxanthine phosphoribosyl transferase; MLCT – medium- and long-chain triacylglycerol (length C8 -C24); OECD – Organisation for Economic Cooperation and Development; TG – test guideline

Table 11. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			IN VITRO		
Triisononanoin	undiluted, 10 µl	EpiSkin™ reconstructed human epidermis model	EPISKIN™ in vitro test, in accord with OECD TG 439; appropriate negative and positive controls were used	predicted to be not irritating	[44]
			ANIMAL		
Triheptanoin	undiluted, 0.5 ml	White Russian rabbits, 6 male	4- h semi-occlusive patches were applied to a 6 cm^2 area performed in accord with OECD TG 404	mean erythema score – 2.22/4; mean edema score – 1.94/4 30-60 min: very slight to well-defined erythema in all animals 24-72 h: moderate to severe erythema and severe edema with brown discolorations and dryness, with sanguineous lacerations and scaling in 1 animal 72 h: 1 animal showed moderate redness of the skin, with dry skin and severe extensive subcutaneous hemorrhage 6 days: scaling was observed in all animals 10-14 days: all animals were normal	[31]
Triheptanoin	undiluted, 0.5 ml	NZW rabbits, 3 males	4- h semi-occlusive patches were applied in accord with OECD TG 404	1 h: very slight and slight erythema in 1 and 2 animals, respectively. 24 h: very slight edema in one of the latter animals very slight and slight erythema in 2 and 1 animals, respectively. 48 h: very slight edema in the latter. 48 and 72 h: very slight erythema in 2 animals, with very slight edema in one	[31]
Triheptanoin	100% for induction and challenge	female Dunkin Hartley guinea pigs, 20 test animals and 10 controls	Buehler test using occlusive patches at induction and challenge	not a sensitizer	[31]
Tristearin	undiluted, 0.5 ml	NZW rabbits, 3 males	4- h semi-occlusive patches were applied to a 6 cm^2 area in accord with OECD TG 404	not irritating no erythema or edema were observed	[32]
Tristearin	50% in petrolatum for induction and challenge	Dunkin Hartley guinea pigs, 20 test animals and 10 controls	Buehler test using occlusive patches at induction and challenge	not a sensitizer	[32]
Caprylic/Capric Triglyceride	undiluted, 0.5 ml	NZW rabbits, 6	4-h semi-occlusive patches	not irritating no erythema or edema were observed	[39]
C8-C12 Acid Triglycerides	undiluted, 0.5 ml	albino rabbits, 3	24-, 48-, and 72-h semi-occlusive application using pieces of soaked “Molton” in accord with OECD TG 404; the application site was 2.5 cm x 2.5 cm	not irritating no erythema or edema were observed	[39]
Triisononanoin	25 and 50% in acetone/oil (4:1 v/v), and undiluted	CBA mice, 4 females	LLNA in accord with OECD TG 429	negative at 25 and 50% (SI = 2.1 and 2.16, respectively) positive at 100% (SI = 4.27); may cause sensitization EC_3 = 70%	[44]
Triisostearin	concentration and vehicle not stated	NZW rabbits, 3 males	4- h semi-occlusive patches were applied to a 6 cm^2 area in accord with OECD TG 404	1 and 24 h: well-defined erythema observed in 3/3 animals 48 h: slight erythema persisted in 2/3 animals 72 h: erythema cleared completely no edema was observed in any animal at any time point	[33]

Table 11. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			HUMAN		
facial oil containing 95.51% Caprylic/Capric Triglyceride	applied neat	17subjects	SIOPT; 24 h patch	not irritating; PII = 0	45
facial oil containing 95.51% Caprylic/Capric Triglyceride		26 subjects	modified maximization test procedure; 5 occlusive patches (2 cm x 2 cm) were applied for 48-72 h; the test sites were pretreated with 0.25% SLS one day prior to patching Challenge was conducted following a 14-day non-treatment period; an occlusive patch with 5.0% SLS was applied for 1 h, followed by application of a test patch for 48 h; controls were patched with a sham patch following SLS pretreatment	not a sensitizer	46
moisturizer containing 6%Tribehenin	applied neat; 0.01 g (pink solid paste)	102 subjects	HRIPT; 24-h occlusive patches (2 cm x 2 cm) were applied to the upper back3 x/wk for 3 wks; challenge was performed following an 8-19 day non-treatment period with a 24-h occlusive patch to a previously untreated site	no adverse events were reported not a sensitizer	47
mixture containing 20%Tribehenin	0.2 g	52 subjects	HRIPT; 24-h occlusive patches (1 in x 1 in) were applied to the upper back3 x/wk for 3 wks; challenge was performed following a 2 wk non-treatment period with a 24-h occlusive patch to a previously untreated site	8 subjects had a response on a least one day of induction, ranging from barely perceptible (+) to moderate (score of 2; 1 occurrence); at challenge, one subject had a mild reaction at the 72 h reading and a barely perceptible reaction with dryness at a 96-h follow-up evaluation the researchers stated that none of these responses were considered clinically significant, and concluded there was no clinically significant potential for dermal irritation or sensitization	48
Triolein	not stated	human subjects; number not stated	chamber test; details not provided	not a sensitizer	35

Abbreviations: HRIPT – human repeated insult patch test; LLNA – local lymph node assay; NZW – New Zealand White; OECD – Organisation for Economic Cooperation and Development; PII – primary irritation index; SI – stimulation index; SIOPT - single insult occlusive patch test; SLS – sodium lauryl sulfate; TG – test guideline

Table 12. Ocular irritation studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			IN VITRO		
Triisononanoin	undiluted, 30 µl	HCE model	In vitro eye irritation test using the SkinEthic™ reconstructed model	predicted to be non-irritating	44
			ANIMAL		
Triheptanoin	undiluted, 0.1 ml	rabbits, 3 males	24 h instillation into one eye	non-irritating	31
Tristearin	undiluted, 0.1 ml	rabbits, 3 males	24 h instillation into one eye in accord with OECD TG 405	non-irritating any effects observed were resolved by day 6	32
Caprylic/Capric Triglyceride	undiluted, 0.1 ml	NZW rabbits, 6	single instillation into one eye; 72-h observation period	non-irritating	39
C8-C12 Acid Triglyceride	undiluted, 0.05 ml	albino rabbits, 3	6 instillations were made on 6 consecutive days; animals were observed for 10 days	non-irritating	39
Triisostearin	concentration and vehicle not stated	NZW rabbits, 3 males	24 h instillation into one eye in accord with OECD TG 405	non-irritating any effects observed were resolved within 48 h	33

Abbreviations: HCE - Human Corneal Epithelium; NZW - New Zealand White; OECD – Organisation for Economic Cooperation and Development; TG – test guideline

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SAFETY DATA SHEET

Revision date 24-August-2022 **Revision Number** 2

1. Identification

Product identifier

Product Name CAPRYLIC/CAPRIC TRIGLYCERIDE

Other means of identification

Product Code(s) C3465

Synonyms None

Recommended use of the chemical and restrictions on use

Recommended use No information available

Restrictions on use No information available

Details of the supplier of the safety data sheet

Supplier Address
Spectrum Chemical Mfg. Corp.
14422 South San Pedro St.
Gardena, CA 90248
(310) 516-8000

Emergency telephone number

Emergency Telephone Chemtrec 1-800-424-9300

2. Hazard(s) identification

Classification

This chemical is not considered hazardous by the 2012 OSHA Hazard Communication Standard (29 CFR 1910.1200).

Hazards not otherwise classified (HNOC)
Not applicable

Label elements

Hazard statements
This chemical is not considered hazardous by the 2012 OSHA Hazard Communication Standard (29 CFR 1910.1200).

The product contains no substances which at their given concentration, are considered to be hazardous to health.

Appearance Clear **Physical state** Liquid **Odor** No information available

Other information
May be harmful if swallowed.

3. Composition/information on ingredients

Substance

Chemical name	CAS No	Weight-%	Trade secret
Caprylic/capric Triglyceride	73398-61-5	100	*

*The exact percentage (concentration) of composition has been withheld as a trade secret.

4. First-aid measures

Description of first aid measures

Inhalation Remove to fresh air.

Eye contact Rinse thoroughly with plenty of water for at least 15 minutes, lifting lower and upper eyelids. Consult a physician.

Skin contact Wash skin with soap and water.

Ingestion Clean mouth with water and drink afterwards plenty of water.

Most important symptoms and effects, both acute and delayed

Symptoms No information available.

Indication of any immediate medical attention and special treatment needed

Note to physicians Treat symptomatically.

5. Fire-fighting measures

Suitable Extinguishing Media Use extinguishing measures that are appropriate to local circumstances and the surrounding environment.

Large Fire CAUTION: Use of water spray when fighting fire may be inefficient.

Unsuitable extinguishing media Do not scatter spilled material with high pressure water streams.

Specific hazards arising from the chemical No information available.

Explosion data

Sensitivity to mechanical impact none.

Sensitivity to static discharge none.

Special protective equipment for fire-fighters Firefighters should wear self-contained breathing apparatus and full firefighting turnout gear. Use personal protection equipment.

6. Accidental release measures

Personal precautions, protective equipment and emergency procedures

Personal precautions Ensure adequate ventilation.

Methods and material for containment and cleaning up

Methods for containment Prevent further leakage or spillage if safe to do so.

Methods for cleaning up Pick up and transfer to properly labeled containers.

7. Handling and storage

Precautions for safe handling

Advice on safe handling Handle in accordance with good industrial hygiene and safety practice.

Conditions for safe storage, including any incompatibilities

Storage Conditions Keep container tightly closed in a dry and well-ventilated place.

8. Exposure controls/personal protection

Control parameters

Exposure Limits The following ingredients are the only ingredients of the product above the cut-off level (or level that contributes to the hazard classification of the mixture) which have an exposure limit applicable in the region for which this safety data sheet is intended or other recommended limit. At this time, the other relevant constituents have no known exposure limits from the sources listed here.

Appropriate engineering controls

Engineering controls Showers
Eyewash stations
Ventilation systems.

Individual protection measures, such as personal protective equipment

Eye/face protection No special protective equipment required.

Skin and body protection No special protective equipment required.

Respiratory protection No protective equipment is needed under normal use conditions. If exposure limits are exceeded or irritation is experienced, ventilation and evacuation may be required.

General hygiene considerations Handle in accordance with good industrial hygiene and safety practice.

9. Physical and chemical properties

Information on basic physical and chemical properties

Physical state	Liquid
Appearance	Clear
Color	Colorless to Yellow

Odor	No information available
Odor threshold	No information available

Property	**Values**	**Remarks • Method**
pH	no data available	None known
Melting point / freezing point	-5 °C / 23 °F	None known
Boiling point / boiling range	150 °C / 302 °F	None known
Flash point	260 °C / 500 °F	None known
Evaporation rate	no data available	None known
Flammability (solid, gas)	no data available	None known
Flammability Limit in Air		None known
Upper flammability or explosive limits	No data available	
Lower flammability or explosive limits	No data available	
Vapor pressure	No data available	None known
Vapor density	no data available	None known
Relative density	0.95	None known
Water solubility	Insoluble in water	None known
Solubility(ies)	Soluble in Oils Soluble in most organic solvents	None known
Partition coefficient	No data available	None known
Autoignition temperature	no data available	None known
Decomposition temperature		None known
Kinematic viscosity	no data available	None known
Dynamic viscosity	No data available	None known

Other information

Explosive properties	No information available
Oxidizing properties	No information available
Softening point	No information available
Molecular weight	No information available
VOC Content (%)	No information available
Liquid Density	No information available
Bulk density	No information available

10. Stability and reactivity

Reactivity No information available.

Chemical stability Stable under normal conditions.

Possibility of hazardous reactions None under normal processing.

Conditions to avoid None known based on information supplied.

Incompatible materials None known based on information supplied.

Hazardous decomposition products None known based on information supplied.

11. Toxicological information

Information on likely routes of exposure

Inhalation Specific test data for the substance or mixture is not available.

Eye contact Specific test data for the substance or mixture is not available.

Skin contact Specific test data for the substance or mixture is not available.

Ingestion May be harmful if swallowed.

Symptoms related to the physical, chemical and toxicological characteristics

Symptoms No information available.

Acute toxicity

Numerical measures of toxicity

Chemical name	Oral LD50	Dermal LD50	Inhalation LC50
Caprylic/capric Triglyceride 73398-61-5	> 5000 mg/kg (Rat)	-	-

Delayed and immediate effects as well as chronic effects from short and long-term exposure

Skin corrosion/irritation No information available.
Serious eye damage/eye irritation No information available.
Respiratory or skin sensitization No information available.
Germ cell mutagenicity No information available.

Reproductive toxicity No information available.

STOT - single exposure No information available.
STOT - repeated exposure No information available.
Aspiration hazard No information available.

Other adverse effects No information available.

Interactive effects No information available.

12. Ecological information

Ecotoxicity .

Chemical name	Algae/aquatic plants	Fish	Toxicity to microorganisms	Crustacea
Caprylic/capric Triglyceride 73398-61-5	-	-	-	EC50: >2.2mg/L (24h, Daphnia magna)

Persistence and degradability No information available.
Bioaccumulation Inherently biodegradable.

Other adverse effects No information available.

13. Disposal considerations

Waste treatment methods

Waste from residues/unused products Dispose of in accordance with local regulations. Dispose of waste in accordance with environmental legislation.

Contaminated packaging Do not reuse empty containers.

14. Transport information

DOT not regulated

TDG	not regulated
MEX	not regulated
ICAO (air)	not regulated
IATA	not regulated
IMDG	not regulated
RID	not regulated
ADR	not regulated
ADN	not regulated

15. Regulatory information

International Inventories

TSCA	Complies
DSL/NDSL	Complies
EINECS/ELINCS	Complies
ENCS	This product complies with ENCS:
IECSC	This product complies with China:
KECL	Complies
PICCS	Complies
AICS	All the constituents of this material are listed on the Australian Inventory of Chemical Substances (AICS).

Legend:
TSCA - United States Toxic Substances Control Act Section 8(b) Inventory
DSL/NDSL - Canadian Domestic Substances List/Non-Domestic Substances List
EINECS/ELINCS - European Inventory of Existing Chemical Substances/European List of Notified Chemical Substances
ENCS - Japan Existing and New Chemical Substances
IECSC - China Inventory of Existing Chemical Substances
KECL - Korean Existing and Evaluated Chemical Substances
PICCS - Philippines Inventory of Chemicals and Chemical Substances

US Federal Regulations

SARA 313
Section 313 of Title III of the Superfund Amendments and Reauthorization Act of 1986 (SARA). This product does not contain any chemicals which are subject to the reporting requirements of the Act and Title 40 of the Code of Federal Regulations, Part 372.

SARA 311/312 Hazard Categories
Should this product meet EPCRA 311/312 Tier reporting criteria at 40 CFR 370, refer to Section 2 of this SDS for appropriate classifications.

CWA (Clean Water Act)
This product does not contain any substances regulated as pollutants pursuant to the Clean Water Act (40 CFR 122.21 and 40 CFR 122.42).

CERCLA
This material, as supplied, does not contain any substances regulated as hazardous substances under the Comprehensive Environmental Response Compensation and Liability Act (CERCLA) (40 CFR 302) or the Superfund Amendments and Reauthorization Act (SARA) (40 CFR 355). There may be specific reporting requirements at the local, regional, or state level pertaining to releases of this material.

US State Regulations

California Proposition 65
This product does not contain any Proposition 65 chemicals.

U.S. State Right-to-Know Regulations
This product does not contain any substances regulated under applicable state right-to-know regulations

U.S. EPA Label Information

EPA Pesticide Registration Number Not applicable

16. Other information

NFPA
Health hazards 0
Flammability 1
Instability 0
Physical and chemical properties -
HMIS
Health hazards 1
Flammability 1
Physical hazards 0
Personal protection X

Key or legend to abbreviations and acronyms used in the safety data sheet
Legend Section 8: EXPOSURE CONTROLS/PERSONAL PROTECTION

TWA	TWA (time-weighted average)	STEL	STEL (Short Term Exposure Limit)
Ceiling	Maximum limit value		

Key literature references and sources for data used to compile the SDS
Agency for Toxic Substances and Disease Registry (ATSDR)
U.S. Environmental Protection Agency ChemView Database
European Food Safety Authority (EFSA)
EPA (Environmental Protection Agency)
Acute Exposure Guideline Level(s) (AEGL(s))
U.S. Environmental Protection Agency Federal Insecticide, Fungicide, and Rodenticide Act
U.S. Environmental Protection Agency High Production Volume Chemicals
Food Research Journal
Hazardous Substance Database
International Uniform Chemical Information Database (IUCLID)
Japan GHS Classification
Australia National Industrial Chemicals Notification and Assessment Scheme (NICNAS)
NIOSH (National Institute for Occupational Safety and Health)
National Library of Medicine's ChemID Plus (NLM CIP)
National Library of Medicine's PubMed database (NLM PUBMED)
National Toxicology Program (NTP)
New Zealand's Chemical Classification and Information Database (CCID)
Organization for Economic Co-operation and Development Environment, Health, and Safety Publications
Organization for Economic Co-operation and Development High Production Volume Chemicals Program
Organization for Economic Co-operation and Development Screening Information Data Set
World Health Organization

Revision date 24-August-2022
Revision Note No information available.
Disclaimer
The information provided in this Safety Data Sheet is correct to the best of our knowledge, information and belief at the date of its publication. The information given is designed only as a guidance for safe handling, use, processing, storage, transportation, disposal and release and is not to be considered a warranty or quality specification. The information

relates only to the specific material designated and may not be valid for such material used in combination with any other materials or in any process, unless specified in the text.

End of Safety Data Sheet