European Food Safety Authority

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SCIENTIFIC OPINION

Calcium caprylate and magnesium caprylate added for nutritional purposes as sources of calcium and magnesium to food supplements [1]

Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food

(Questions No EFSA-Q-2008-017, EFSA-Q-2008-018)

Adopted on 5 June 2009

PANEL MEMBERS

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SUMMARY

Following a request from the European Commission to the European Food Safety Authority, the Scientific Panel on Food Additives and Nutrient Sources added to Food (ANS) was asked to evaluate the safety of calcium caprylate and magnesium caprylate and the bioavailability of calcium and magnesium from these sources respectively, added for nutritional purposes to food supplements.

The exposure to supplemental caprylate based on the proposed uses and use levels might amount to nearly 6 g caprylate/day from calcium caprylate and to nearly 3 g caprylate from magnesium caprylate, equivalent to 95 mg/kg bw/day from calcium caprylate and to 49 mg/kg bw/day from magnesium caprylate. The proposed use levels would provide doses of 800 mg calcium/day and 250 mg magnesium/day from the respective sources, which are below or in line with the established Tolerable Upper Intake Levels (ULs) for calcium and magnesium. Altogether, intake of caprylate from food supplements might amount to nearly 9 g caprylate/day which is equivalent to 145 mg/kg bw/day for a 60 kg person.

[1] For citation purposes: Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food on calcium caprylate and magnesium caprylate as a source of calcium and magnesium added for nutritional purposes to food supplements, following a request from the European Commission. *The EFSA Journal* (2009) 1146, 1-20.

Caprylic acid is a natural component of the diet usually esterified in the form of triacylglycerol, which is found in the fat content of dairy products such as milk (0.3 %) and butter (0.8 %), and also in palm kernel oil (3-4 %) and coconut oil (9-10 %).

The average dietary exposure to caprylate is considered to be in the range of 330 to 410 mg/day, and at high percentile dietary exposure up to 992 mg/day.

Calcium caprylate and magnesium caprylate are salts of a medium-chain fatty acid. They are insoluble in water but would be expected to dissociate in the acidic environment of the stomach and the bioavailability of the respective cations is expected to be similar to that of other, soluble sources of these cations.

There were no toxicological data on calcium caprylate or magnesium caprylate in the dossiers. Few toxicological data are available on caprylic acid while several studies have been performed with triglycerides containing different percentages of caprylates.

Caprylic acid exhibited no mutagenic activity in microbial mutation assays. The Panel concluded that the molecule has no structural alert for genotoxicity and that the data available do not raise concern with respect to genotoxicity.

The Panel considered whether studies in animals with triglycerides could provide a basis for the assessment of caprylic acid according to the percentage of caprylic acid present in the triglycerides tested. A 91-day study performed on the triglyceride caprenin in mice allowed the derivation of a No-Observed-Adverse-Effect-Level (NOAEL) equal to 3036 and 3358 mg/kg bw/day of caprylate for male and female mice respectively. The Panel identified a NOAEL from the 2-year NTP (1994) study on rats exposed to the triglyceride tricaprylin at 2.5 mL/kg bw/day, equivalent to approximately 2400 mg/kg bw/day of tricaprylin and 1900 mg/kg bw/day of caprylate. The NTP study (1994) appears to be the more relevant for risk assessment of caprylic acid than the 91-day study in mice. Using the NOAEL of 1900 mg/kg bw/day for caprylate would result in a Margin Of Safety of 12, in relation to the estimated exposure from the proposed uses, which the Panel would consider inadequate. However, the Panel noted that the effects in the forestomach observed in the NTP study (which were the basis for the NOAEL) might be specific for tricaprylin in rats and should not therefore be extrapolated to caprylic acid.

The proposed use levels would result in exposures to caprylic acid around 10- to 30-fold higher than the estimated exposure to caprylate from the diet.

The Panel considers that since the exposures from the proposed use levels for calcium caprylate and magnesium caprylate are not comparable to the estimated dietary exposures for caprylic acid, and would result from a single bolus dose, it is not possible to assume that there would be sufficient capacity to handle this load of caprylic acid using normal metabolic pathways. However, the Panel notes that the nutrients are only 7-12 % by weight of the caprylate, so if calcium and magnesium were administered at the UL, exposure to caprylic acid from the sources would be significant, both in absolute weight and in calorific terms.

The Panel concludes that there are insufficient toxicological data on caprylic acid itself to allow conclusions on the safety of the proposed use and use levels of calcium caprylate and magnesium caprylate. The Panel notes that read across from the tricaprylin data would result in inadequate safety margins but concludes that such a read across is inappropriate since the forestomach effect may result from tricaprylin and not caprylic acid. Nevertheless, the caprylin data could indicate possible concerns about caprylic acid. Also, the Panel highlights the paucity of toxicological data on caprylic acid, and considers that long term toxicity data on caprylic acid would be needed for an adequate assessment. The Panel concludes that the

amounts of caprylic acid from the proposed use levels are far greater than dietary exposures and it is therefore not possible to base a safety evaluation on the normal metabolism of dietary caprylic acid.

The Panel therefore concludes that the safety of calcium caprylate and magnesium caprylate, as sources of calcium and magnesium respectively, at the proposed use levels cannot be established based on the available information.

Key words:

Magnesium caprylate, CAS Registry Number: 3386-57-0, calcium caprylate, CAS Registry Number: 6107-56-8, nutrient source, caprylic acid, octanoic acid, CAS Registry Number: 124-07-2.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

The European Community legislation lists nutritional substances that may be used for nutritional purposes in certain categories of foods as sources of certain nutrients.

The Commission has received a request for the evaluation of calcium caprylate and magnesium caprylate added for nutritional purposes to food supplements. The relevant Community legislative measure is:

- Directive 2002/46/EC of the European Parliament and of the Council on the approximation of the laws of the Member States relating to food supplements[2].

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority to provide a scientific opinion, based on its consideration of the safety and bioavailability of calcium caprylate and magnesium caprylate added for nutritional purposes in food supplements.

ACKNOWLEDGEMENTS

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[2] OJ L 183, 12.7.2002, p.51.

ASSESSMENT

1. Introduction

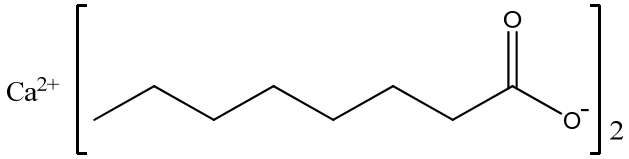
The present opinion deals only with the safety of calcium caprylate and magnesium caprylate as sources of calcium and magnesium respectively, and with the bioavailability of calcium and magnesium from the respective sources. The safety of calcium and magnesium in terms of amounts that may be consumed is outside the remit of this Panel.

2. Technical data

2.1. Chemistry

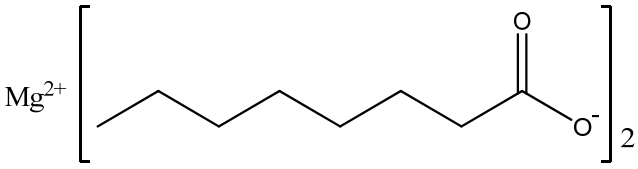
Calcium caprylate:

The CAS Registry Number for calcium caprylate is 6107-56-8. Synonyms are calcium 1-heptanecarboxylate and octanoic acid, calcium salt. The molecular weight of calcium caprylate is 326.47 g/mol; the molecular formula is $Ca(C_8H_{15}O_2)_2$.



Magnesium caprylate:

The CAS Registry Number for magnesium caprylate is 3386-57-0. Synonyms are magnesium 1-heptanecarboxylate and octanoic acid, magnesium salt. The molecular weight of magnesium caprylate is 310.69 g/mol; the molecular formula is $Mg(C_8H_{15}O_2)_2$.



2.2. Specifications

Calcium caprylate is described by the petitioner as a powder, insoluble in water, with a content of 12.28 % calcium. Microbiological contaminants are less than 3000 cfu/g for total plate count, less than 300 cfu/g for yeast and molds, and negative for *Escherichia coli*, *Salmonella* and *Staphylococcus*.

Magnesium caprylate is described by the petitioner as a powder, insoluble in water, with a content of 7.8 % magnesium. Loss on drying is less than 6 %. Heavy metals are no more than 1 mg/kg for lead, arsenic, mercury and cadmium. Microbiological contaminants are less than 3000 cfu/g for total plate count, less than 300 cfu/g for yeast and molds, and negative for *E. coli, Salmonella* and *Staphylococcus*.

2.3. Manufacturing process

Calcium caprylate

Calcium caprylate is manufactured synthetically from a reaction between calcium hydroxide and caprylic acid.

$$Ca(OH)_2 + 2C_8H_{16}O_2 = Ca(C_8H_{15}O_2)_2 + 2\ H_2O$$

Stoichiometric quantities of calcium hydroxide and caprylic acid in water are weighed out. The calcium hydroxide is slowly added to the solution of the caprylic acid. The reaction is taken to completion, after which the product is dried and milled.

Magnesium caprylate

Magnesium caprylate is manufactured synthetically from the reaction between magnesium oxide and caprylic acid.

$$MgO + 2\ C_8H_{16}O_2 = Mg(C_8H_{15}O_2)_2 + H_2O$$

Stoichiometric quantities of magnesium oxide and caprylic acid in water are weighed out. The magnesium oxide is slowly added to the solution of the caprylic acid. The reaction is taken to completion, after which the product is dried and milled.

2.4. Methods of analysis in food

Infrared (IR) spectrometry is a common method for identifying compounds. A sample of calcium caprylate or magnesium caprylate is finely ground and examined using a suitable diamond (Attenuated Total Reflection) ATR device and a Fourier Transform InfraRed (FTIR) spectrometry; results for the test substance are compared with those for a reference standard.

2.5. Reaction and fate in foods to which the source is added

According to the petitioner, calcium caprylate and magnesium caprylate are stable in foods.

2.6. Case of need and proposed uses

Calcium caprylate and magnesium caprylate are used by food supplement manufacturers as ingredients in tablets, caplets, capsules, chewable tablets, effervescent powders and liquids that are food supplements. The method of incorporation of calcium caprylate and magnesium caprylate is determined by the individual manufacturers as appropriate for the particular type of finished products.

The petitioner indicates that the quantity of calcium caprylate or magnesium caprylate to be added to food supplements will be determined by individual formulators, but it is normally the quantity to supply up to 800 mg/day of calcium and up to 250 mg magnesium/day (adults) respectively.

2.7. Information on existing authorisations and evaluations

No documents have been provided by the petitioner on risk assessment evaluations of calcium and magnesium caprylate.

According to the petitioner, calcium caprylate and magnesium caprylate have been in use as ingredients in food supplement products legally on sale in the UK since 12th July 2002.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated the safety of caprylic acid as a flavouring substance in 1999, and concluded that it is not of safety concern when used as flavour (WHO, 1999).

The JECFA evaluation on octanoic acid-containing formulations concluded that the estimated exposure from use in antimicrobial solutions posed no safety concerns (WHO, 2004).

Caprylic acid (octanoic acid) has been assessed by the Food Standards Australia New Zealand (FSANZ, 2005) for use as a processing aid. The highest exposure to caprylic acid from this source was 3.5 mg/day. It was concluded that there would be no toxicological concerns if permission was granted for approval of caprylic acid as a processing aid. They concluded the Margin Of Safety to be sufficient to consider that the use of caprylic acid as a processing aid is not of safety concern.

In Commission Directive 2002/72/EC of 6 August 2002 relating to plastic materials and articles intended to come into contact with foodstuffs (EC, 2002) caprylic acid is permitted as a monomer (No 14320) and as an additive (No 41960) with no specific migration limit based on a Scientific Committee for Food (SCF) classification as List 0 (food ingredient) (SCF, 1999).

In 1993 the SCF established the Population Reference Intakes (PRI) for calcium. More recent reports on calcium intake (IOM, 1997; D-A-CH, 2000; AFSSA, 2001) include the attainment of peak bone mass during childhood, adolescence and young adulthood in their calculations. The Adequate Intakes (AI) and Recommended Daily Intakes (RDI) thus derived are generally higher than the PRI. They are between 500 and 800 mg calcium per day for children up to the age of 7 years, 1200 to 1300 mg calcium per day for older children and adolescents, and 900 to 1200 mg calcium per day for adults (SCF, 2003).

The SCF has issued opinions on the Tolerable Upper Intake Level (UL) for calcium (SCF, 2003) and magnesium (SCF, 2001). The ULs were 2500 mg calcium/day from all sources for adults and 250 mg magnesium/day for readily dissociable magnesium salts and compounds

like magnesium oxide, not including magnesium normally present in foods and beverages, for adults and children aged 4 years and older.

2.8. Exposure

In Table 1 and Table 2 information on the intake of calcium, magnesium and caprylate from food, anticipated exposures by using calcium and magnesium caprylates as proposed by the petitioner and ULs are summarised.

Exposure to calcium caprylate:

Foods that are particularly rich in calcium include milk (1200 mg/kg), cheese (730-12000 mg/kg) and other dairy products (except butter), green leafy vegetables (except spinach), soybean products, bread and other baked goods made from calcium-fortified flour (variable levels), almonds (2400 mg/kg), brazil nuts (1700 mg/kg) and hazelnuts (1400 mg/kg). In European diets 45 to 70 % of calcium intake is from milk and dairy products (SCF, 2003).

According to the SCF (2003) the average and 97.5th percentile calcium intakes from food in European countries vary from 683 to 944 mg/person/day and from 1421 to 1970 mg/person/day, respectively (Table 1).

To supply 800 mg of calcium per day (see section 2.6) the exposure to calcium caprylate would be 6513 mg/day, corresponding to 109 mg/kg bw/day for a 60 kg body weight adult and the exposure to caprylate would be 5753 mg/day, equivalent to 96 mg/kg bw/day for a 60 kg body weight adult (Table 1).

Table 1. **Summary information on calcium intake and anticipated exposure to caprylate from calcium caprylate**

Calcium	**Amount (mg/day)**	**P97.5 (mg/day)**	**References**
Recommended Daily Intake for adults	700		SCF, 1993
Tolerable Upper Intake Level (UL) for adults	2500 (all sources)		SCF, 2003
Intake range from food	683-944	1421-1970	SCF, 2003
Highest amount of calcium as supplement indicated by the petitioner	800		Present dossier
Total anticipated exposure to calcium from supplements and food intake	1483-1744	2221-2770	Calculated by Panel
Source: Caprylate			
Intake range from food	331-410	696-992	FSANZ, 2005 Hulshof *et al.,* 2004
Intake from other uses (processing aid)	1.1-1.6	2.5-3.5	FSANZ, 2005
Highest amount of caprylate as supplement indicated by the petitioner	5753	5773	Present dossier
Total anticipated exposure to caprylate from supplements, other uses and food intake	6084-6163	6459-6775	Calculated by Panel

Exposure to magnesium caprylate:

Magnesium is ubiquitous in foods, but its content varies substantially. Leafy vegetables, as well as grains and nuts generally have higher magnesium contents (60-2700 mg/kg) than meats and dairy products (less than 280 mg/kg). Fats, refined sugars and pure alcohol do not contain magnesium. Meat, most kinds of fish, fruit, most vegetables and dairy products contain less than 250 mg of magnesium/kg wet weight. Cacao and bitter chocolate, conches, shrimps, soybeans, butter beans, and beet greens contain over 1000 mg of magnesium/kg. The magnesium content of grain and grain products largely depends on processing: high concentrations (1100-1800 mg/kg) are found in whole barley, whole rye, wheat flour or brown rice (EVM, 2003; SCF, 2001).

According to the SCF (2001), the average and 97.5th percentile magnesium intakes from food in European countries vary from 208 to 353 mg/person/day and from 350 to 628 mg/person/day, respectively.

To supply 250 mg of magnesium per day (see section 2.6), the exposure to magnesium caprylate would be 3189 mg/day, corresponding to 53 mg/kg bw/day for a 60 kg body weight adult and the exposure to caprylate would be 2975 mg/day, equivalent to 49 mg/kg bw/day for a 60 kg body weight adult (see Table 2).

Table 2. **Summary information on magnesium intake and anticipated exposure to caprylate from magnesium caprylate**

Magnesium	**Amount (mg/day)**	**P97.5 (mg/day)**	**References**
Acceptable range of intake for adults	150-500		SCF, 1993
Tolerable Upper Intake Level (UL) for adults	250 supplemental use		SCF, 2001
Intake range from food	208-353	350-628	SCF, 2001
Highest amount of magnesium as supplement indicated by the petitioner	250		Present dossier
Total anticipated exposure to magnesium from supplements and food intake	458-603	600-878	Calculated by Panel
Source: Caprylate			
Intake range from food	331-410	696-992	FSANZ, 2005 Hulshof *et al*., 2004
Intake from other uses (processing aid)	1.1-1.6	2.5-3.5	FSANZ, 2005
Highest amount of caprylate as supplement indicated by the petitioner	2975	2975	Present dossier
Total anticipated exposure to caprylate from supplements, other uses and food intake	3306-3385	3671-3967	Calculated by Panel

Exposure to caprylate:

Caprylic acid, also known as octanoic acid, is a medium chain saturated fatty acid that occurs naturally in foods, usually esterified in the form of triacylglycerol. Caprylic acid is found in dairy products such as milk (0.3 %) and butter (0.8 %), and also in palm kernel oil (3-4 %) and coconut oil (9-10 %).

According to the petitioner, there is little information on exposure to caprylic acid. Estimates were provided for Australia (whole population aged 2 years and above (n=13 858) and children aged 2-6 years (n=989) and New Zealand (whole population aged 15 years and

above (n=4 636)) (FSANZ, 2005). The assessment was based on dietary survey data using a 24-hour food recall methodology. Estimated mean dietary exposures to caprylic acid were 331 mg/day for Australian children aged 2-6 years, 365 mg/day for the whole Australian population and 399 mg/day for the New Zealand population studied. Estimated 95th percentile dietary exposure to naturally occurring caprylic acid was the lowest for Australian children aged 2-6 years at 696 mg/day, and the highest for New Zealanders aged 15 years and above, at 992 mg/day. Including dietary exposure to caprylic acid as a processing aid (see section 2.7) would have a minimal effect on the predicted dietary exposures to caprylic acid from natural sources (FSANZ, 2005). The Panel notes that these estimates are more or less in line with reported results in the Netherlands. In the 1997/1998 Dutch National Food Consumption Survey, using a 2-day dietary record method, mean exposure from natural sources ranged from 170 mg/day (girls aged 1-3 years, n=119) to 410 mg/day (males aged 51-70 years, n=511). At the 95th percentile the exposure varied from 380 mg/day (girls 1-3 years old) to 930 mg/day (males aged 51-70^{+} years). For the overall population aged 1 year and older (n= 6 250) an exposure of 350 mg/day on the average and 770 mg/day at the 95th percentile was reported (Hulshof *et al.,* 2004).

The exposure to supplemental caprylate based on the proposed uses and use levels of calcium caprylate and magnesium caprylate might amount to nearly 6 g caprylate/day from calcium caprylate (Table 1) and to nearly 3 g caprylate from magnesium caprylate (Table 2), equivalent to 95 mg/kg bw/day from calcium caprylate and to 49 mg/kg bw/day from magnesium caprylate. Altogether, intake of caprylate from supplements might amount to nearly 9 g caprylate/day which is equivalent to 145 mg/kg bw/day for a 60 kg person. The Panel notes that this is about 10- to 30-times higher compared to the estimated dietary intake of caprylate.

3. Biological and toxicological data

3.1. Bioavailability

There are no data in the dossier on the bioavailability of the cations from these nutrient sources. Calcium caprylate and magnesium caprylate are salts of a medium-chain fatty acid. According to the petitioner, the salts are insoluble in water but they are expected to dissociate in the acidic environment of the stomach and the bioavailability of the respective cations is expected to be similar to that for other, soluble sources of these cations.

3.2. Biological fate and biological distribution

Short-chain and medium-chain fatty acids such as caprylic acid are absorbed from the intestine into the systemic circulation. These fatty acids are readily broken down to carbon dioxide and two-carbon fragments and do not undergo resynthesis to triacylglycerols. These fatty acids serve as a ready source of energy (Molkentin *et al.,* 2000).

Medium-chain triglycerides are partially hydrolysed by lingual lipase in the stomach and are rapidly and efficiently hydrolysed by pancreatic lipase within the intestinal lumen, thereby allowing for the direct absorption of medium-chain fatty acid. Aliphatic linear carboxylic acids are metabolised in the fatty acid β-oxidation pathway, the tricarboxylic acid cycle, or the C_1-tetrahydrofolate pathways.

3.3. Toxicological data

Calcium caprylate and magnesium caprylate

No toxicological data are provided on calcium caprylate or magnesium caprylate.

Caprylate

A 14-day acute toxicity 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). The only indications of toxicity in surviving animals noted by the investigators were depression and diarrhoea.

Caprylic acid exhibited no mutagenic activity in microbial mutation assays (*Saccharomyces cerevisiae* D4 and *Salmonella typhimurium* TA 97, TA 98, TA 100, TA 1535, TA 1537, TA 1538) with and without metabolic activation (Brusick, 1976; Zieger *et al*., 1988).

Sprague Dawley rats (n=16/group) gavaged on gestation days 6-15 with caprylic acid in corn oil at dose levels of 0, 1 125 or 1 500 mg/kg bw/day exhibited maternal toxicity (rale and dyspnea) and maternal mortality (21 % and 44 % respectively). Most deaths occurred shortly after dosing and were attributed to the respiratory effect of the treatment. However, according to the authors, the high percentage of deaths could have been due to tracheal intubation. There was a decrease in the number of live pups on post-gestational day 6, while no teratogenic effect was observed (Narotsky *et al.,* 1994).

Medium-chain triglyceride (containing caprylic acid)

Subchronic toxicity

Caprenin, a triglyceride comprising caprylic (C8:0), capric (C10:0), and behenic (C22:0) acids, was administered in a semi-purified diet to weanling Sprague-Dawley rats (n=25/sex/group) at dose levels of 5.23, 10.23 or 15.00 % (w/w) for 91 days. Corn oil was added at 8.96, 5.91 and 3.00 %, respectively, to provide essential fatty acids and digestible fat calories. Corn oil alone (12.14 %) and a blend of medium-chain triglyceride (MCT) oil (11.21 %) plus corn oil (3.13 %) served as controls. All diets were formulated to provide about 4000 kcal/kg of diet and 26.8 % of digestible calories from fat, assuming that corn oil, MCT oil, and caprenin provided 9, 7 and 5 kcal/g, respectively. Survival, clinical signs, body weight, feed consumption, feed efficiency, organ weights, organ-to-body-weight ratios, organ-to-brain-weight ratios, haematological values and clinical chemistry parameters were evaluated in all groups. Histopathology of a full complement of tissues was evaluated in the corn oil and MCT oil control groups as well as the high-dose caprenin group. Additional rats (n=5/sex/group) were included in the study to determine whether there was marked storage of behenic acid (C22:0) in the heart, liver or perirenal fat at the end of the 91-day feeding period. No significant differences in body weight gain were measured although feed conversion efficiency was reduced in the high-dose caprenin group. No adverse effects from the ingestion of caprenin were detected, nor were significant amounts of behenic acid (C22:0) present in the fat extracted from the selected fat depot sites (Web *et al*., 1993).

These results establish a No-Observed-Adverse-Effect Level (NOAEL) of more than 15 % (w/w) caprenin in the diet (or more than 83 % of total dietary fat), which is equal to a mean exposure level of more than 13.2 g/kg bw/day of caprenin for male rats and more than 14.6 g/kg bw/day of caprenin for female rats. As there is only 23 % of caprylate in caprinin, the NOAEL for caprylate from this study could be calculated as equal to 3036 and 3358 mg/kg bw/day, respectively (Web *et al.,* 1993).

Genotoxicity and carcinogenicity

Tricaprylin (a triglyceride in which all three fatty acids are C8, caprylic acid, 81 %) was mutagenic in strain TA 1535 in the presence of hamster or rat S9, but only at very high concentrations (6 666 to 16 666 µg/plate) and not without S9. Tricaprylin did not induce mutations in strains TA 97, TA 98 and TA 100 with or without S9 (NTP, 1994).

The US National Toxicology Program (NTP) designed studies to evaluate the role of several oils in altering cancer rates in male rats. The NTP study was designed to determine the mechanism by which corn oil induces pancreatic cancer. Corn oil, safflower oil and tricaprylin (a triglyceride in which all three fatty acids are C8, caprylic acid, 81 %) were administrated by gavage to male F344/N rats 5 days per week for 2 years at volumes of 0, 2.5, 5 or 10 mL/kg bw equivalent for tricaprylin to 0, 2375, 4750 and 9500 mg/kg bw/day respectively corresponding to 0, 1923, 3847 and 7695 mg caprylic acid/kg bw/day.

The 2-year survival rate of high-dose tricaprylin administered to male rats was lower than that of the control rats (0 mL/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 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 in 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 in the 0, 2.5, 5 and 10 mL/kg groups, respectively). According to the NTP study, there was a clear increase in incidence of squamous cell papillomas in the forestomach (19 %) in rats receiving 10 mL tricaprylin/kg with multiple papillomas occurring in two rats. All except one of the papillomas were found at the end of the study. There was a pronounced increase in incidence of basal hyperplasia (38 %) in the 10 mL tricaprylin/kg group, which did not appear to be in response to irritation of the forestomach as there was very little evidence of inflammation or other toxicity.

The incidence of nephropathy was significantly decreased in high-dose rats in comparison to the control, 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 the 0, 2.5, 5 and 10 mL/kg groups, respectively). In high dose group rats, the incidence of mononuclear cell leukaemia was decreased (23/50, 28/50, 22/50, 9/53 in the 0, 2.5, 5 and 10 mL/kg groups, respectively) in comparison to the control. There were no significant increases in carcinomas found in this study.

There was not a statistically significant difference in any of the observed parameters between untreated control and 2.5 mL/kg/bw groups.

The Panel considered that the NOAEL of this study for tricaprylin is 2.5 mL/kg bw/day, equivalent to approximately 2.4 g/kg bw/day of tricaprylin and 1.9 g/kg bw/day of caprylate (NTP, 1994).

Reproduction and developmental studies

According to Traul *et al.* (2000), in a study with Sherman albino rats fed diets containing 20 % lard or MCT, in addition to 0.09 % linoleic acid for 10 to 12 months, no effect on fertility was noted.

In a reproductive toxicity study, young adult male and female Wistar rats were fed a balanced diet containing 19.6 % of a MCT, consisting of 75 % caprylic and 25 % capric acid, for 3 weeks before mating. This group was compared to concurrent groups fed high oleo oil, butter fat or coconut oil diets. Body weight gain, 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 compared to those on the other diets. 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 weight gains comparable to that of control rats on the other diets. There were no adverse effects on reproductive parameters or on pup development except for slightly lower body weight gains during the lactation period (Harkins and Sarett, 1968).

The Panel considered that the NOAEL for MCT from this reproduction study is 19.6 % of the diet equivalent to 19.6 g/kg bw/day and 14.7 g/kg bw/day of caprylic acid.

Human data

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; each formula derived 40 % of its caloric content from fat. The study lasted for 10 weeks and used a crossover study design. The MCT-containing diet and the corn oil-containing diet 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 bw (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 hours after consuming the MCT preparation. No toxicological symptoms were reported (CTFA, 1980).

4. Discussion

There were no toxicological data on calcium caprylate or magnesium caprylate provided in the dossiers. Few toxicological data are available on caprylic acid while several studies have been performed with triglycerides containing different percentages of caprylates.

Caprylic acid exhibited no mutagenic activity in microbial mutation assays (*Saccharomyces cerevisiae* D4 and *Salmonella typhimurium* TA 97, TA 98, TA 100, TA 1535, TA 1537, TA

1538) with and without metabolic activation (Brusick, 1976; Zieger *et al*., 1988). Tricaprylin (a triglyceride in which all three fatty acids are C8, caprylic acid) was mutagenic in strain TA 1535 in the presence of hamster or rat S9, but only at very high concentrations (6 666 to 16 666 µg/plate) and not without S9. Tricaprylin did not induce mutations in strains TA 97, TA 98 and TA 100 with or without S9 (NTP, 1994).

The Panel concluded that the molecule has no structural alert for genotoxicity and that the data available do not raise concerns with respect to genotoxicity. The Panel considered whether studies in animals with triglycerides could provide a basis for the assessment of caprylic acid according to the percentage of caprylic acid present in the triglycerides tested. The 91-day study performed on the triglyceride caprenin in mice allowed the derivation of a NOAEL equal to 3036 and 3358 mg/kg bw/day caprylate for male and female mice respectively. From the 2-year NTP study on rats exposed to the triglyceride tricaprylin at 2.5 mL/kg bw/day, the Panel identified a NOAEL equivalent to approximately 2400 mg/kg bw/day tricaprylin and 1900 mg/kg bw/day caprylate (NTP, 1994).

In comparison to the 91-day study, the NTP study is more recent, of longer duration and the percentage of caprylic acid in the triglyceride tested is higher; the NOAEL derived from the NTP study is lower than that from the 91-day study. Consequently, the NTP study (NTP, 1994) would appear to be more relevant for risk assessment of caprylic acid than the 91-day study (Web *et al.,* 1993). Using the NOAEL of 1900 mg/kg bw/day for caprylate would result in a Margin Of Safety of 12 in relation to the estimated exposure from the proposed uses, which the Panel would consider inadequate. However, the Panel noted that the effects in the forestomach observed in the NTP study (which were the basis for the NOAEL) might be specific for tricaprylin in rats and should not therefore be extrapolated to caprylic acid.

Caprylic acid is a natural component of the diet usually esterified in the form of triacylglycerol; it is found in the fat content of dairy products such as milk (0.3 %) and butter (0.8 %), and also in palm kernel oil (3-4 %) and coconut oil (9-10 %).

The average dietary exposure to caprylate is considered to be in the range of 330 to 410 mg/day, and at high percentile dietary exposure up to 992 mg/day.

The Panel noted that caprylate (octanoic acid) is a normal dietary constituent, absorbed from the intestine to the portal circulation, rapidly metabolised into carbon dioxide and two-carbon fragments and is without any structural alert for genotoxicity. If exposures based on the proposed use levels were comparable to dietary exposure estimates, then the Panel would consider that these arguments could provide a reasonable basis for evaluation of the safety of caprylic acid. However, the Panel notes that the nutrient is only 7-12 % by weight of the caprylate, so if calcium as calcium caprylate and magnesium as magnesium caprylate were administered at the UL, then exposure to caprylic acid from the source would be significant both in absolute weight and in calorific terms. The proposed use levels would result in exposures to caprylic acid around 10- to 30-fold higher than the estimated exposure to caprylate in the diet. The Panel considers that since the exposures from the proposed use levels are not comparable to dietary exposures and that they result from a single bolus dose, it is not possible to assume that there would be sufficient capacity to handle this load using normal metabolic pathways.

CONCLUSIONS

The present opinion deals only with the safety of calcium caprylate and magnesium caprylate as sources of calcium and magnesium, respectively and with the bioavailability of calcium and magnesium from the respective sources. The safety of calcium and magnesium in terms of amounts that may be consumed is outside the remit of this Panel.

Calcium caprylate and magnesium caprylate are salts of a medium-chain fatty acid. They are insoluble in water but expected to dissociate in the acidic environment of the stomach and the bioavailability of the respective cations is expected to be similar to that of other, soluble sources of these cations.

The Panel concludes that there are insufficient toxicological data on caprylic acid itself to allow conclusions on the safety of the proposed use and use levels of calcium caprylate and magnesium caprylate. The Panel notes that read across from the tricaprylin data would result in inadequate safety margins but concludes that such a read across is inappropriate since the forestomach effect may result from tricaprylin and not caprylic acid. Nevertheless the caprylin data indicate possible concerns about caprylic acid. The Panel highlight the paucity of toxicological data on caprylic acid, and considers that a long term toxicity data on caprylic acid would be needed for an adequate assessment. The Panel concludes that the amounts of caprylic acid from the proposed use levels for calcium caprylate and magnesium caprylate are far greater than dietary exposures and it is therefore not possible to base a safety evaluation for supplemental calcium caprylate and magnesium caprylate on the normal metabolism of dietary caprylic acid. The Panel therefore concludes that the safety of calcium caprylate and magnesium caprylate as sources of calcium and magnesium respectively cannot be established.

DOCUMENTATION PROVIDED TO EFSA

1. Dossier on Calcium caprylate proposed for Addition to Annex II of Directive 2002/46/EC of the European Parliament and of the Council Relating to Food Supplements. December 2007. Submitted by Gee Lawson Ltd.
2. Dossier on Magnesium caprylate proposed for Addition to Annex II of Directive 2002/46/EC of the European Parliament and of the Council Relating to Food Supplements. December 2007. Submitted by Gee Lawson Ltd.

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GLOSSARY / ABBREVIATIONS

AFSSA	Agence Française de Sécurité Sanitaire des Aliments
AI	Adequate Intakes
ANS	Panel on Food Additives and Nutrient Sources added to Foods
ATR	Attenuated Total Reflection
bw	body weight
CAS	Chemical Abstracts Service
EC	European Commission
EFSA	European Food Safety Authority
EVM	Expert group on Vitamins and Minerals
FTIR	Fourier Transform InfraRed
IR	Infrared
JECFA	Joint FAO/WHO Expert Committee on Food Additives
MCT	Medium-Chain Triglyceride
MOS	Margin Of Safety
NOAEL	No-Observed-Adverse-Effect Level
NTP	National Toxicology Program
IOM	Institute of Medicine
PRI	Population Reference Intakes
SCF	Scientific Committee on Food
RDI	Recommended Daily Intakes
UL	Tolerable Upper Intake Level
WHO	World Health Organisation