

**Opinion of the Scientific Panel on Food Additives, Flavourings,
Processing Aids and Materials in Contact with Food on**

**Sucrose esters of fatty acids, E 473 and sucroglycerides, E 474
based on a request from the Commission related to
Sucrose Esters of Fatty Acids (E 473)**

Question number EFSA-Q-2003-139

Adopted on 7 October 2004

Modified on 25 January 2006

SUMMARY

The Scientific Panel on food additives, flavourings, processing aids and materials in contact with food has been asked to re-evaluate the safety of sucrose esters of fatty acids (E 473).

Sucrose esters of fatty acids, E 473 (and sucroglycerides, E 474, which are a mixture of sucrose esters of fatty acids and mono-, di- and triglycerides from edible fats or oils) are food additives permitted in the European Union for use as emulsifiers and stabilisers for oil/water emulsions in several processed foods by Directive 95/2/EC on food additives other than colours and sweeteners.

The EC Scientific Committee for Food (SCF) considered sucrose esters of fatty acids (together with sucroglycerides) in 1992. The SCF established a group ADI of 0-20 mg/kg bw (expressed as sucrose monostearate) for sucrose esters of fatty acids and sucroglycerides derived from palm oil, lard and tallow fatty acids, providing that specifications would limit the presence of tetra and higher esters to no more than 7%.

The re-evaluation was requested in the light of new studies on short- and long-term toxicity in experimental animals as well as toxicokinetic studies in animals and humans. In addition, studies on laxative effects in humans had been provided.

Sucrose esters of fatty acids have low oral toxicity and do not raise concern of carcinogenicity. Metabolic studies *in vitro* and in rats, dogs and humans show that these esters are extensively hydrolysed in the gastrointestinal tract into well-known food constituents prior to absorption, that only small amounts of intact monoesters are absorbed, and that incompletely hydrolysed sucrose esters appear to be excreted in the faeces. It is unlikely that di- and higher esters are absorbed intact. There is no evidence of tissue accumulation of the absorbed monoesters.

They are completely metabolised to carbon dioxide or integrated into other endogenous constituents.

From the new 2-year chronic toxicity/carcinogenicity study a NOAEL can be established at 5% sucrose esters of fatty acids in the diet of rats, equal to 1970 mg/kg bw/day in males. The sucrose esters of fatty acids tested was composed of sucrose esters of stearic and palmitic acids (70:30) with a high content of tetra- and higher esters (10%). The main effects seen in rats in previous long-term studies on sucrose esters of fatty acids containing lower levels of higher esters at very high doses ($\geq 10\%$ dietary levels) were a tendency towards lower body weights, soft stool and diarrhoea. The NOAEL of 2000 mg/kg bw/day from the new long-term rat study.

Concern about a potential laxative effect in humans was raised by results from an inadequate study in which laxation and related abdominal symptoms were reported in humans ingesting doses of sucrose esters of fatty acids exceeding 2g/day equivalent to 33 mg/kg bw/day. In a subsequent well designed and conducted human tolerance study no adverse effects were observed in men and women receiving divided daily doses of 1.5 g sucrose esters of fatty acids in bread for 5 days (equal to 27 mg/kg in men and 29 mg/kg in women). However, this was the only dose level tested, and it was lower than the dose range (33 – 75 mg/kg bw/day) reported to produce gastrointestinal symptoms in the first study.

Considering all the toxicity data with an overall NOAEL of 2000 a group ADI of 40 mg/kg bw/day can be established for sucrose esters of fatty acids (E 473) and sucroglycerides (E 474). However, in view of the human tolerance studies the Panel wishes to point out that at daily doses above 2 g/day in adults these substances may cause gastrointestinal symptoms. This ADI covers products containing mono-, di- and triesters with a content of tetra and higher esters of no more than 10%.

Conservative estimates of chronic intake of sucrose ester of fatty acids (E 473) and sucroglycerides (E 474) in the adult population were above 20 mg/kg bw/day at the 95th percentile. In young children, conservative estimates of the chronic intake approach the ADI. Refined chronic intake estimates are needed. Based on current Maximum Permitted Levels, for a variety of foods and beverages, a single eating occasion would lead to intakes of sucrose esters of fatty acids (E 473) and sucroglycerides (E 474) in the range of 1 g. High intakes on a one day basis could therefore be expected, particularly in children.

Taking both the new rat studies and the human tolerance studies into consideration a group ADI of 40 mg/kg bw/day was established for sucrose esters of fatty acids (E 473) and sucroglycerides (E 474).

KEY WORDS

Sucrose esters of fatty acids, sucroglycerides, E 473, E 474, food additive, emulsifier, stabiliser.

BACKGROUND

Sucrose esters of fatty acids, E 473 (and sucroglycerides, E 474, which are a mixture of sucrose esters of fatty acids and mono-, di- and triglycerides from edible fats or oils) are food additives permitted in the European Union for use as emulsifiers and stabilisers for oil/water emulsions in several processed foods by Directive 95/2/EC on food additives other than colours and sweeteners.

Sucrose esters of fatty acids (and sucroglycerides) were considered by the EC Scientific Committee for Food (SCF) in 1992. The SCF established a group ADI of 0-20 mg/kg bw (expressed as sucrose monostearate) for sucrose esters of fatty acids and sucroglycerides derived from palm oil, lard and tallow fatty acids, providing that specifications would limit the presence of tetra and higher esters to no more than 7%. The basis for establishing the numerical ADI was not specified and no report was issued (SCF, 1992).

In 2002 the Scientific Committee on Food (SCF) was asked by the European Commission to re-evaluate the safety of sucrose esters of fatty acids (E 473) in the light of new studies on short- and long-term toxicity in experimental animals as well as kinetic studies in animals and humans.

The evaluation could not be completed under the SCF mandate and continuation of this work now falls to the EFSA Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food.

TERMS OF REFERENCE

The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food is asked to re-evaluate the safety of sucrose esters of fatty acids (E 473).

ASSESSMENT

• Chemistry

Sucrose esters of fatty acids consist of a mixture of mono- di- and triesters of sucrose with food fatty acids. The fatty acids form esters with the hydroxyl groups in the sucrose molecule and in principle one sucrose molecule could accommodate a total of eight fatty acid molecules. (FAO, 1997a).

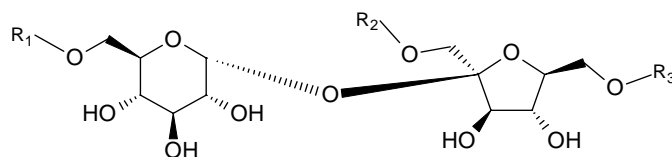


Figure. Chemical structure of sucrose esters. A tri-ester is depicted. Groups R₁, R₂ and R₃ usually comprise mixed residues of C_{14:0}, C_{16:0}, C_{18:0} and/or C_{18:1} fatty acids.

Sucroglycerides consist of a mixture of mono-, di-, and triesters of sucrose and fatty acids together with mono-, di-, and triglycerides from the edible fat or oil used in the production of the sucroglycerides (EU, 1996; FAO, 1997b).

- **Specifications**

Specifications for sucrose esters of fatty acids and sucroglycerides are provided in the Directive 96/77/EEC as amended by 98/86/EEC.

The most recent specifications for sucrose esters of fatty acids (not less than 80% sucrose esters) and for sucroglycerides (not less than 40% and not more than 60% of sucrose esters) have been prepared by Joint FAO/WHO Expert Committee on Food Additives (JECFA) at its 49th meeting in 1997 (FAO 1997a,b). Appropriate limits for the solvents used in the manufacturing process are provided.

- **Manufacturing process**

Sucrose esters of fatty acids are either prepared from sucrose and methyl or ethyl esters of food fatty acid or by extraction from sucroglycerides. The following solvents can be used for the production: dimethyl formamide, ethyl acetate, isopropanol, propylene glycol, isobutanol and methyl ethyl ketone. Sucroglycerides are obtained by reacting sucrose with an edible fat or oil with or without the presence of a solvent. The following solvents can be used: dimethyl formamide, cyclohexane, isobutanol, isopropanol and ethylacetate (EU, 1996; FAO1997a,b).

- **Existing authorisations and evaluations**

Sucrose esters of fatty acids, E 473 (and sucroglycerides, E 474, which is a mixture of sucrose esters of fatty acids and mono-, di- and triglycerides from edible fats or oils) are permitted in the European Union as food additives in a wide range of processed foods by Directive 95/2/EC on food additives other than colours and sweeteners. They are approved to be used at *quantum satis* in dietary food supplements and for surface treatment of fresh fruit and with Maximum Permitted Levels varying from 1 to 20 g / kg in other foods. In particular they are authorised for use at 5 g/kg in desserts, dairy based drinks, edible ices and sugar confectionery and at 10 g/kg in fine bakery wares and sauces. E 473 is also authorised for use in infant formulae for infants in good health with a Maximum Permitted Level of 120 mg/l in

products containing hydrolysed proteins, peptides or aminoacids. Moreover, E 473 is authorised *quantum satis* for use as carrier for colours and for fat soluble antioxidants.

Sucrose esters of fatty acids (and sucroglycerides) were considered by the EC Scientific Committee for Food (SCF) in 1992. The SCF established a group ADI of 0-20 mg/kg bw (expressed as sucrose monostearate) for sucrose esters of fatty acids and sucroglycerides derived from palm oil, lard and tallow fatty acids, providing that specifications would limit the presence of tetra and higher esters to no more than 7%. The SCF “was not satisfied however that the toxicity data could be used to provide assurance of safety for products derived from other feedstocks or based on other fatty acids and recommended that the specifications be drafted to exclude such products. In order to establish the safety of these products, satisfactory biochemical data would be required to indicate the degree to which the esters were broken down and absorbed in the gut and, in the case of any products derived from rapeseed oil, that the feedstocks were low in erucic acid. The satisfactory results of mutagenicity tests would be required if hydrolysis in the gut proved to be incomplete”. The basis for establishing the numerical ADI was not specified by the SCF and no report was issued (SCF 1992).

The safety of sucrose esters of fatty acids and sucroglycerides has also been evaluated by JECFA several times. Data evaluated by JECFA prior to the SCF evaluation in 1992 showed that sucrose esters of fatty acids have a low oral toxicity and do not raise concern of carcinogenicity. Metabolic studies *in vitro* and *in vivo* indicated that these esters are hydrolysed in the gastrointestinal tract into well-known food constituents prior to absorption. There is no evidence of tissue accumulation of these esters and incompletely hydrolysed sucrose esters appear to be excreted in the faeces. From all available data it was concluded that a 3% dietary level does not cause toxic effects in rats or dogs. The main effects in rats, at very high doses ($\geq 10\%$ dietary level), were a tendency towards lower body weights, soft stool and diarrhoea. At its 44th meeting in 1995, JECFA allocated a temporary group ADI of 0-20 mg/kg bw to sucrose esters of fatty acids and sucroglycerides based on a NOEL of 5% sucrose esters of fatty acids in the diet of rats (equal to 1970 mg/kg bw/day) in a long-term toxicity/carcinogenicity study. The sucrose esters of fatty acids tested was composed entirely of sucrose esters of stearic and palmitic acids (70:30). JECFA stressed that the evaluation applied to sucrose esters of fatty acids prepared from palmitic, stearic, and oleic acids, as well as palm oil, lard, and tallow. Due to concern about laxation and related abdominal symptoms observed in an inadequate human tolerance study, JECFA made the ADI temporary and requested the results of a well designed and conducted tolerance study for review in 1997(WHO, 1995). This study was submitted and evaluated by JECFA in 1997 at its 49th meeting, where a full group ADI of 0-30 mg/kg bw was established for sucrose esters of fatty acids and sucroglycerides (WHO, 1998).

- **Exposure**

Verger *et al.* (1998) have estimated the overall Theoretical Maximum Daily Intake of sucrose esters of fatty acids (E 473) and sucroglycerides (E 474) for France: 8 mg/kg bw/day at the mean and 17 mg/kg bw/day at the 95th percentile. The estimate was based on the combination of food consumption data derived from household purchase data in France with the Maximum Permitted Level in all foods according to the existing EU authorisations.

Conservative estimates of the intake of sucrose esters of fatty acids and sucroglycerides were provided to the Commission by France, The Netherlands and UK (European Commission, 2001). These estimates are based on actual national food consumption data, assuming that the additives are used in the widest possible range of foods at Maximum Permitted Level. In young children (under 3 years, standard body weight of 15 kg) estimates varied from 45 to 75 mg/kg bw. Since conservative estimates for the adult population were above the ADI (20 mg/kg bw.), refined intake estimates were deemed necessary for both adults and children.

On the basis of Maximum Permitted Levels, it appears that standard portions of different foods and beverages may lead to high intakes of E 473 and E 474. Thus, either a single portion of fine bakery ware (100 g) or a glass of dairy based drink (200 ml) may lead to the intake of 1 g of E 473 or E 474, equivalent to 33 mg/kg bw in a 30 kg child.

BIOLOGICAL AND TOXICOLOGICAL DATA

The toxicological data on sucrose esters of fatty acids generated prior to the SCF evaluation in 1992 (SCF, 1992) and the JECFA evaluation in 1995 (WHO, 1995) has been summarised by the petitioner and is presented in Annex 1.

The new data on sucrose esters of fatty acids submitted by the petitioner were studies on the absorption, distribution, metabolism and excretion (ADME) in rats, dogs and humans, a 13-week toxicity study in rats, a two-year combined chronic feeding and carcinogenicity study in rats, and a laxative study in healthy human volunteers. The test compounds used in the new studies were Ryoto Sugar Esters S-570 and S-1170.

S-570 is a mixture consisting of 28% monoesters, 34% diesters, 21% triesters, and 10% tetra and higher esters with a fatty acid composition containing about 70% stearic acid and 30% palmitic acid.

S-1170 is a mixture consisting of 57% monoesters, 28% diesters, 10% triesters, and 1% tetra and higher esters with a fatty acid composition containing about 70% stearic acid and 30% palmitic acid.

Absorption, distribution, metabolism and excretion

Kinetic studies of sucrose esters of fatty acids have been performed in rats, dogs and humans (Mitsubishi 1994a; 1994b). The test substances in the studies using non-radiolabelled compounds were sucrose monostearate (SMS, 99% pure) or two mixtures with different compositions of sucrose esters of fatty acids, i.e. S-570 and S-1170 (see composition above).

In the studies with labelled compounds sucrose 1-¹⁴C-monostearate (¹⁴C-SMS, radiochemical purity of 98.6% - 99.0% or more) and sucrose ¹⁴C-distearate (¹⁴C-SDS, radiochemical purity of 99.0% - 100%) were used.

- *Rat studies*

Four studies have been performed in male and female F344 rats (Mitsubishi, 1994a).

In the first study, bioavailability of sucrose monostearate (SMS) was investigated by measuring plasma levels of SMS after single oral (5, 100 and 200 mg/kg bw) or intravenous (1 mg/kg bw) administration of SMS to four male rats. SMS was also administered as a single oral dose to four female (100 mg/kg bw) rats. At varying time intervals, during 24 hours after dosing, blood samples were collected for analysis of plasma SMS concentrations by GC-MS. Plasma levels of SMS declined to below the limit of detection (0.01 µg/mL plasma) 24 hours after administration in all groups. After oral administration dose related peak plasma concentrations (C_{max}) in males were reached between 1 and 2 hours. The area under the plasma concentration versus time curve ($AUC_{0 \rightarrow \infty}$) were 0.40, 0.71 and 1.23 µg•hr/mL (5, 100 and 200 mg/kg bw respectively). There was a monophasic elimination with half lives between 2.4 and 4.1 hours. In contrast, after intravenous administration a biphasic elimination was observed with elimination half-lives of 0.41 hours for the first phase and 6.9 hours for the second and an $AUC_{0 \rightarrow \infty}$ of 2.39 µg•hr/mL. The oral bioavailability (after correction to dose equivalence) of SMS in the male rats was 0.026-0.033%. The C_{max} (0.28 cf. 0.13 µg/mL) and $AUC_{0 \rightarrow \infty}$ (1.68 cf. 0.71 µg•hr/mL) in females were higher but the elimination half-life of 2.9 hours and time to peak plasma concentration of 2 hours were similar (Mitsubishi, 1994a).

In the second study, plasma and organ tissue levels of sucrose monostearate (SMS) and sucrose monopalmitate (SMP) were determined after 4-weeks of daily oral administration of Ryoto Sugar Ester S-570 in rats. Diets containing 1% and 5% of S-570 were fed *ad libitum* to groups of four male rats for 1, 2 or 4 weeks. The 4 weeks feeding group included additional groups for studies of 3 days, 1 week and 2 weeks recovery. The mean intakes of S-570 after 1, 2, 3 and 4 weeks of treatment in the 1% group were 720, 690, 640 and 590 mg/kg bw and day, respectively, and in the 5% group 3670, 3520, 3370 and 3030 mg/kg and day, respectively.

After the various treatment periods SMP and SMS were measured in the plasma, liver, kidney, heart, spleen, lung and white (perirenal) fat. In the groups fed 1% of S-570 the SMP

concentrations remained almost constant in plasma and tissues during the 4 weeks and were close to or below the limits of detection (0.01-0.06 µg/g). At the 5% level slightly increased levels of SMP were seen with similar amounts detected at the various sampling points, with the highest concentrations in the liver (0.3-0.4 µg/g) followed by the kidney, lung, spleen, heart and plasma.

SMS could be detected in plasma and tissues at both dose levels proportional to the dose administered. At the 1% dose level SMS levels remained almost constant in all tissues after 7, 14 or 28 days of dosing, whereas at the 5% dose level, the tissue concentrations in the liver, spleen and lung increased with duration of treatment. The highest concentration found (after 4 weeks at the 5% dose level) was in the liver (5.65 µg/g), followed by the white fat (1.27 µg/g), lung (1.05 µg/g), kidney (0.96 µg/g), spleen (0.64 µg/g) and heart (0.26 µg/g). At the 5% dose level, the retention ratios (tissue content in relation to the final daily dose) determined after 7, 14 and 28 days of treatment (SMS intake 742-899 mg/kg bw and day; SMP intake 318-385 mg/kg bw and day) were 4-5 fold higher for SMS than for SMP in the liver and kidney, and 2-3 folds for the heart, spleen and lung. The retention in the liver of SMS and SMP (combined) after 4 weeks at the 5% dose level was 0.018-0.031%. SMP and SMS levels of all tissues were below the limit of detection 3 days after completion of the 28-day treatment (Mitsubishi, 1994a).

In the third study, which was performed as a part of a chronic toxicity and carcinogenicity study (see below), plasma and liver concentrations of SMP and SMS were measured in 5 rats per sex and group after 2-years of daily oral administration of Ryoto Sugar Ester S-570. The rats had been fed S-570 at 1% (males 338 mg/kg bw/day, females 411 mg/kg bw/day), 3% (males 939 mg/kg bw/day, females 1124 mg/kg bw/day) and 5% (males 1684 mg/kg bw/day, females 2182 mg/kg bw/day) for 2 years. The actual intakes of S-570 were measured during the final week of the study.

Plasma SMP concentrations were below or close to the detection limit at all dose levels whereas the plasma levels of SMS in the 1%, 3% and 5% dose groups were 0.03, 0.05 and 0.15 µg/mL and 0.02, 0.08 and 0.06 µg/mL in males and females, respectively. The concentrations of SMP (0.01-0.09 µg/g) and SMS (0.11-0.63 µg/g) in the liver were dose dependent in both males and females. The retention in the liver of SMS and SMP (combined) at the 5% dose level were 0.039-0.063%, which is comparable to the results obtained in the previously described 4 week study. Thus, there was no time dependent accumulation of sucrose monoesters in the liver (Mitsubishi, 1994a).

In the fourth study the absorption, distribution, metabolism and excretion (ADME) of SMS and sucrose distearate (SDS) was determined after administration of single oral doses of 100 mg/kg bw of ¹⁴C-SMS or ¹⁴C-SDS to male rats in groups of three.

Radioactivity in the blood peaked 3 hours after the administration of ¹⁴C-SMS (equivalent to 12.0 µg SMS/mL) and ¹⁴C-SDS (equivalent to 8.36 µg SDS/mL), and thereafter declined in a

biphasic manner. The elimination half-life for the first and second phase was approximately 33.2 hours (at 8 to 48 hours) and 96.9 hours (at 48 to 168 hours), respectively. Within 24 hours after dosing 1.4%, 30.8% and 28.7 of ^{14}C -SMS were excreted in urine, faeces and expired air, respectively. The corresponding percentages for ^{14}C -SDS were 0.7%, 63.0% and 13.3%. Thus, at 24 hours after administration the total excretion of ^{14}C -SMS and ^{14}C -SDS was 60.9% and 76.9%, respectively. After 168 hours the total cumulative excretion by these routes had increased to 72.6% for ^{14}C -SMS and 84.9% for ^{14}C -SDS. At 168 hours the radioactivity retained in the carcass was 17.9% of the administered ^{14}C -SMS and 9.2% of the administered ^{14}C -SDS.

The biliary excretion of radioactivity after oral single dose administration of ^{14}C -SMS or ^{14}C -SDS at 100 mg/kg bw was studied in groups of three bile-duct cannulated male rats. For both compounds, the cumulative biliary excretion during 48 hours was 0.1% or less of the dose. The corresponding urinary and faecal excretions were 0.5% and 8.9% for ^{14}C -SMS, and 0.1% and 15.5% for ^{14}C -SDS, respectively.

The tissue distribution of radioactivity was studied at 24 and 168 hours after administration of ^{14}C -SMS or ^{14}C -SDS in a separate study. Each test compound was orally administered to three male rats at 100 mg/kg bw. The plasma peak concentration of ^{14}C -SMS (equivalent to 16.9 μg SMS/mL) and ^{14}C -SDS (equivalent to 7.66 μg SDS/mL) appeared in this study at 2 and 4 hours after the administration, respectively, thereafter declining with an elimination half-life of 34 hours and 40 hours, respectively, reaching 1.9% and 7.6% of the peak concentration at 168 hours, respectively. The number of tissues retaining radioactivity increased with time. At 24 hours after administration of ^{14}C -SMS and ^{14}C -SDS the highest level of radioactivity (% of dose) was found in the liver (8.50% and 3.70%, respectively), followed by skin, muscle, white fat, blood and kidney. At 168 hours the radioactivity of ^{14}C -SMS was still high in white fat (6.11%), muscle (4.97%), skin (2.66%), liver (0.42%), kidney (0.18%) and pancreas (0.16%). At the same point in time, a corresponding high activity of ^{14}C -SDS was found in white fat (2.87%), muscle (2.31%), skin (1.57%), liver (0.25%), and pancreas (0.09%).

Urine, faeces, plasma and various tissues were analysed for SMS, SDS and potential metabolites. After ^{14}C -SMS administration only low levels of unchanged SMS (less than 0.01% of the administered dose) were detected, with the highest concentrations found in the liver (0.051-0.060%) and lungs (0.01-0.02%) at 2 and 4 hours after administration. After ^{14}C -SDS administration, unchanged SDS was not detected in these tissues or in the blood. A small amount of the total radioactivity excreted at 24 hours in the urine (1.4% of dose) and faeces (2.0% of dose) was unchanged SMS. Similarly, after ^{14}C -SDS administration unchanged SDS could be detected in the urine (2.2% of the administered radioactivity) and faeces (39% of the administered activity), as well as a minor amount of SMS in the faeces (4.3% of the administered activity). Altogether six metabolites were determined, but the structures were not elucidated. The major faecal metabolite (87% of the radioactivity) after ^{14}C -SMS

administration was identified as stearic acid. Similarly, stearic acid could be detected in the faeces (50% of activity) after administration of ^{14}C -SDS (Mitsubishi, 1994a).

- *Dog studies*

Kinetic studies were conducted in three male beagle dogs given S-1170 in a single gelatine capsule at doses of 50, 250 and 1250mg/kg bw in that order, separated by a washout period of 7 days between the low and mid doses and a period of 12 days between the mid and high doses. The increasing doses of S-1170 contained 9, 44 and 221 mg/kg bw of SMP and 21, 103 and 515 mg/kg bw of SMS. After administration of the test substance blood concentrations of SMP and SMS were intermittently followed during 48 hours. The time to peak plasma concentration increased with dose and was 3.3-4.7 hours for SMP and 3.3-7.3 hours for SMS. Plasma concentrations of SMP and SMS also increased dose dependently (0.06-0.60 $\mu\text{g}/\text{mL}$ for SMP and 0.12-1.14 $\mu\text{g}/\text{mL}$ for SMS). SMP and SMS at the 250 and 1250 mg/kg bw doses were eliminated from the plasma in a monophasic manner, with a half-life of 2.5 and 5.6 hours for SMP, respectively, and 7.2 and 7.3 hours for SMS, respectively. The $\text{AUC}_{0 \rightarrow \infty}$ was 0.22, 1.37 and 5.10 $\mu\text{g}\cdot\text{hr}/\text{mL}$ for the increasing doses of SMP and 1.76, 5.03 and 15.38 $\mu\text{g}\cdot\text{hr}/\text{mL}$ for the increasing doses of SMS (Mitsubishi, 1994a).

- *Human studies*

Two human studies have been performed in order to evaluate the kinetic characteristics and safety of S-1170 in humans (Mitsubishi, 1994a; Mitsubishi, 1994b). In one of the studies (Mitsubishi, 1994b), the volunteers were also observed for clinical symptoms and subjected to physical examination and laboratory tests (see toxicological section).

In the first study, the kinetics of S-1170, mixed in 200 mL of orange juice, was evaluated in healthy male volunteers (body weights ranged from 51.5 to 70 kg) after single- or multiple-dose regimens. In the single-dose experiment 1, 2 or 3 g of S-1170 was given to 3, 6 and 3 subjects, respectively. In the multiple-dose experiment 1 g of S-1170 was administered to five subjects twice daily (2 g/day) for 5 days.

At 2 and 6 hours after the single-dose administration, SMS and SMP were detected in the plasma (0.01-0.04 $\mu\text{g}/\text{mL}$) at levels close to the detection limit (0.01 $\mu\text{g}/\text{mL}$). At 24 hours SMS was still detectable in 50% of the subjects that received 2g.

In the multiple-dose experiment SMP showed the same pattern with daily levels below 0.03 $\mu\text{g}/\text{mL}$ at 2 hours, and not detectable levels at 24 hours after the last dose. SMS was detected at slightly higher levels and the concentration seemed to increase with number of doses, i.e. the mean concentration after the second daily dose was 0.02, 0.02, 0.05, 0.05 and 0.06 $\mu\text{g}/\text{mL}$ on days 1 to 5, respectively. The SMS levels at 15 and 24 hours after the last dose were 0.05 and 0.02 $\mu\text{g}/\text{mL}$, respectively.

Twelve-hours urine samples were analysed for SMP, SMS, SDE (sucrose distearate) and STE (sucrose tristearate), but these unchanged compounds could not be detected in urine after single or repeated oral administration. The total 48-hour faecal excretion (% of dose) of these sucrose esters was 22%, 25% and 31% at single doses of 1, 2 and 3 g, respectively. The total 120 hour faecal excretion (% of dose) of these sucrose esters after the repeated dose administration was 17%. These results indicate that following ingestion about 70-80% of the sucrose esters are hydrolysed in the gastro-intestinal tract of humans. .

S-1170, at final concentrations of 0.05%, 0.25% or 0.5%, was incubated with cultures of human intestinal flora at 37 °C for 5 hours. After the incubation period, analysis of the total remaining unchanged sucrose esters (SMP, SMS, SDE and STE) showed that 52%, 68% and 67% had been hydrolysed to sucrose and free fatty acids following the incubations at concentrations of 0.05%, 0.25% and 0.5%, respectively (Mitsubishi, 1994a).

Degradation of S-1170, at a concentration of 1.25 mg/mL, was also studied in artificial gastric juice (pH 1.2) at 37 °C for 5 hours. After the incubation the residue levels of SMP, SMS, SDE and STE were 82.7%, 92.8%, 99.8% and 84.4%, respectively. When SMP and SMS were similarly incubated, at concentrations of 0.4 mg/mL, 82% of SMP and 85% of SMS remained (Mitsubishi, 1994a).

In a supplementary study, the kinetics of S-1170, mixed in bread, was studied in healthy male volunteers (age 20-29 years, body weights 60±10 kg) after single or multiple dosing regimens. In the single dose experiment 1, 1.5 or 2 g of S-1170 was given to five subjects per dose group. In one of the multiple dose experiments, bread containing 1.5 g of S-1170 was ingested by five subjects three times daily (4.5 g/day) for 1 day (total dose 4.5 g) or 7 days (total dose 31.5 g). In another multiple dose experiment, bread containing 1 g of S-1170 was given to five subjects two or three times daily (total dose 2 or 3 g/day) for 5 days (total dose 10 or 15 g) (Mitsubishi, 1994b).

In the single dose experiments SMP and SMS could be detected in the plasma at 2 hours (0.01-0.03 µg/mL) after ingestion of 2 g. The peak concentrations of SMP (0.02-0.04 µg/mL) and SMS (0.07-0.11 µg/mL) were detected at 6 hours after the intake. At 24 hours only SMS could be detected in plasma (0.01 µg/mL) and only in a few subjects given 2 g.

In the multiple dose experiments plasma levels of SMP and SMS gradually increased during the first days, reaching a steady state from day 3 and onwards with levels in the range of 0.08-0-14 µg/mL for SMP and 0.20-0.33 µg/mL for SMS. At 24 hours after the last dose SMS, but not SMP, could still be detected in plasma from 3 of 5 subjects (0.02-0.11 µg/mL) (Mitsubishi, 1994b).

- **Toxicological data**

- *Short-term toxicity studies*

Sucrose esters of fatty acids, S-570, was fed for 13 weeks to groups of 20 male and female F344/DuCrj rats at 0, 1%, 3%, and 5% in the diet, equal to 636, 1990, or 3240 mg/kg bw/day in males and 666, 1950, or 3430 mg/kg bw/day in females (Mitsubishi 1991). The animals were observed daily and physical examinations and determination of body weights and food consumption were performed weekly. Haematological and clinical chemistry parameters were measured in blood samples taken from all animals at termination. Urinalysis parameters were measured prior to termination in 10 rats/sex/group and ophthalmological examinations were conducted on 10 rats/sex/group prior to treatment and on 10 rats/sex from the control and high-dose groups before termination. Gross necropsy was performed on all animals at termination and organ weight were recorded for liver, kidneys, adrenals, testes, ovaries, brain, heart, lungs and spleen. Histopathological examinations were carried out on 44 tissues and organs in all control and high-dose animals. Animal tissues showing macroscopic changes in the low- and mid-dose groups were also examined histopathologically.

Administration of the test compound caused no adverse clinical signs or consistent effects on body weights, food consumption or food efficiency. No macroscopic, organ weight or histopathological changes were observed which could be attributed to the treatment. There were no significant toxicological effects on haematological, clinical chemistry and urinalysis parameters. However, albumin was increased in males at the mid- and high-doses, but these findings could not be related to other abnormalities. Moreover, a non-significant, increase in GPT was noted in males at the mid- and high-dose and in females at the high dose. The increase was however within the range of the control values for the animals, and regarded to be of minor importance since no relevant histological changes were noted in the liver.

- *Long-term toxicity/carcinogenicity studies*

A combined chronic oral toxicity (14 rats/sex/dose for 52 weeks) and carcinogenicity study (50 rats/sex/dose for 104 weeks) was performed in Fischer 344/Du Crj rats (Mitsubishi, 1994c). The rats were fed a diet containing Ryoto Sugar Ester S-570 at 0, 1%, 3% or 5% in the diet equal to 394, 1160, or 1970 mg/kg bw/day in males and 480, 1440 or 2440 mg/kg bw/day in females. Adequate observations, physical and ophthalmological examinations, body weight and food consumption recordings as well as haematological and clinical chemistry examinations were carried out throughout the study. Gross necropsy was performed on all animals at termination and organ weights were recorded for liver, kidneys, adrenals, testes, ovaries, brain, heart, lungs and spleen. Histopathological examinations were carried out on 48 tissues and organs in all control and high-dose animals and in animal tissues showing macroscopic changes in the low- and mid-dose groups.

Survival at 52 (100%) and 104 weeks (66-76%) was not affected by the treatment with S-570. Food efficiency was not affected by S-570, but an initial reduction in food intake in males and females was observed for a few weeks in the mid- and high-dose groups. A reduced body weight gain ($\geq 97\%$ of controls) was observed with random incidence during the first 49

weeks in males receiving 5% test material. However, during the second year of the study body weight progression was normal.

Statistically significant increases in the mean corpuscular volume (MCV) affecting mainly the high-dose males and females were observed at many of the sampling points. In addition, sporadic significant decreases were seen in red blood cell count, haemoglobin concentration, mean corpuscular haemoglobin concentration (MCHC) and platelet count. However, although statistically significant these changes were small and not considered toxicologically significant by the authors. No effects of the treatment were seen in the clinical chemistry parameters or at the ophthalmological examinations.

At termination of the 104 weeks study absolute and relative spleen weights were significantly increased in males at 3% and 5% and in females at 3% (but not in females at 5%). The changes in spleen weight and haematological parameters were most likely caused by the occurrence of large granular lymphocyte (LGL) leukaemia. Aged rats of this strain normally have a high incidence of LGL leukaemia that can be as high as 24% for males and 25% for females. In this experiment, the LGL leukaemia frequencies in the groups receiving 0%, 1%, 3% and 5% of test material were 7/50, 9/50, 11/50 and 12/50 in males and 10/50, 7/50, 14/50 and 13/50 in females, respectively. Thus, LGL leukaemia was a common neoplasm in all groups but was slightly increased without statistical significance at the two top doses. However, when the rats that showed LGL leukaemia were removed from the spleen weight determinations, no differences were seen between treated and control rats. In that case, the spleen weights of the rats treated with S-570 at concentrations of 0% 1%, 3% or 5% in the diet were 1.3, 1.3, 1.4 and 1.6 g in males 0.6, 0.7, 0.8 and 0.6 g in females, respectively. Consistent with the higher incidence of LGL leukaemia in the high-dose group, there were associated non-neoplastic findings; extramedullary haematopoiesis in the spleen and haematopoietic hyperplasia in the bone marrow was slightly (but not significantly) increased in the high-dose groups.

The incidences of other neoplastic and non-neoplastic changes were not affected by the treatment with S-570. Thus, the NOAEL in the 104 weeks study was 5% S-570 in the diet, equivalent to 1970 mg/kg bw/day in males and 2440 mg/kg bw/day in females (Mitsubishi, 1994c; Takeda and Flood, 2002)

Special studies in humans

In the studies on the kinetic properties of S-1170 in healthy human volunteers subjective symptoms were recorded throughout the study period and physical examinations were conducted and changes in haematology, clinical chemistry, and urinalysis were monitored (Mitsubishi, 1994a; 1994b).

No clinical symptoms were observed in the three persons who received a single dose of 1 g S-1170 in 200 mL orange juice, but after single doses of 2 g and 3 g S-1170 soft stools or diarrhoea were observed in 4/6 and 3/3 subjects, respectively. The incidence and severity of

these symptoms increased with dose. When 5 individuals ingested 1 g twice daily (2 g/day) for 5 days no clinical symptoms developed.

After a single dose of 1.5 g or 2 g of S-1170, administered in bread, treatment related soft stool or diarrhoea were observed in 1/5 or 3/5 of the subjects, respectively. No symptoms of laxation were observed in the volunteers who ingested 1 g of S-1170 in bread. In the multiple-dose studies, treatment related increases in laxation were observed in 4/5 subjects receiving 1.5 g three times daily for 7 days (1-5 events), in 2/5 persons receiving 1 g three times daily for 5 days, and in 1/5 subjects receiving 1 g two times daily for 5 days. Treatment related clinical symptoms, besides laxation, were a feeling of enlarged abdomen, borborygmus, abdominal pain, flatus, suprapubic discomfort and nausea. These abdominal symptoms, noted during 1 to 10 h after the administration, were transient and slight and tended to subside by 24 hours. There were no treatment-related changes in the results of physical examinations or in haematology, clinical chemistry urinalysis parameters (Mitsubishi, 1994b).

To further evaluate the laxative effects of S-1170, an oral tolerance study using a double-blind, cross-over design was conducted on an in-patient basis. Ten men and ten women, age 21-35 years, participated. Twice daily for 5 days they consumed a serving of bread containing 0.75 g of S-1170 (mean daily dose 27 mg/kg b.w. in males and 29 mg/kg b.w. in females) or control bread. After a 6-day interval the treatment groups were reversed for the next 5 days treatment period. In addition to these time periods, subjects were monitored for 2 days prior to the treatment and for 2 days following the last treatment. Study conditions were closely controlled with respect to hours of walking and sleeping, food and water consumption, smoking and intake of alcohol, caffeine and medications. Subjective symptoms and frequency and appearance of faeces were recorded. Blood pressure, pulse, breathing rate, body temperature, body weight and a standard set of haematological, clinical chemistry and urinalysis parameters were recorded prior to administration of the test substance and after the end of the treatment periods at day 7. Medical examinations were conducted on each subject daily.

There was no treatment-related effect on the frequency of faecal excretion either in males or females. Incidents of changes in faecal consistency (“muddy” or “watery”) occurred in a few subjects, whereas “soft” faeces lasting for 1 to 4 days was observed in several subjects regardless of whether they were consuming control bread or S-1170 containing bread. No treatment-related effects were recorded at day 7 (1½ days after the final dose) in blood pressure, pulse, breath rate, body temperature and body weight, or in the standard battery of haematological, clinical chemistry and urinalysis parameters (Mitsubishi, 1996).

- **Discussion**

The Panel noted that data evaluated by JECFA prior to the SCF evaluation in 1992 (and presumably used by the SCF in its evaluation) showed that sucrose esters of fatty acids had a

low oral toxicity and did not raise concerns about carcinogenicity. Metabolic studies *in vitro* and *in vivo* indicated that these esters were hydrolysed in the gastrointestinal tract into well-known food constituents prior to absorption. There was no evidence of tissue accumulation of these esters and incompletely hydrolysed sucrose esters appeared to be excreted in the faeces. From all available data it was concluded that a dietary level of at least 3% did not cause toxic effects in rats or dogs. The main effects in rats, at very high doses ($\geq 10\%$ dietary level), were a tendency towards lower body weights, soft stool and diarrhoea.

Since the evaluation performed by SCF in 1992 (SCF, 1992) new kinetic studies in rats, dogs and humans, short- and long-term/carcinogenicity studies in rats, and human tolerance studies have become available on sucrose esters of fatty acids. The materials used in these new studies (S-570 and S-1170) were of a slightly different composition than the test mixtures used in the previous studies, which consisted mainly of mono- and diesters, together with traces of triesters. The test material administered to rats in the new studies (S-570) was a mixture consisting of 28% monoesters, 34% diesters, 21% triesters, and 10% tetra and higher esters, whereas the material given to dogs and humans (S-1170) was a mixture consisting of 57% monoesters, 28% diesters, 10% triesters, and 1% tetra and higher esters, both with a fatty acid composition containing about 70% stearic acid and 30% palmitic acid. The higher content of triesters and higher esters in the test materials used in the rat studies would address the concerns of toxicity from such esters expressed in the previous evaluation by the SCF.

In accordance with the results of many older studies it can be concluded from the new studies that sucrose esters of fatty acids do not produce significant toxicological effects, including carcinogenicity, in rats at dietary intakes up to 1970 mg/kg bw/day in males and 2440 mg/kg bw/day in females for two years.

Studies on the disposition of sucrose esters of fatty acids in rats, dogs, and humans including studies using radioactively labelled sucrose monopalmitate (SMP), and mono- and distearate (SMS and SDS) in the experimental animals showed that only small amounts of the intact monoesters were absorbed, and that absorption of intact diesters could not be measured. The monoesters absorbed were completely metabolised into carbon dioxide or integrated into other endogenous constituents. Within 24 hours after administration of radiolabelled SMS and SDS to rats about 61% and 77% of the radioactivity, respectively, had been excreted in urine, faeces and expired air. In humans, only 20-30% of single doses of sucrose esters of fatty acids (S-1170) were retrieved as intact esters from the faeces after 48 hours, whereas the total human faecal excretion of intact sucrose esters after 5 daily treatments was 17%. This suggests a high rate of hydrolysis in the gastrointestinal tract, in accordance with the finding that more than 50% of sucrose esters were hydrolysed within 5 hours in cultures of the human intestinal microflora. Degradation of various sucrose esters of fatty acids in gastric juice was limited.

It is evident that there is only a low level of absorption of the intact sucrose monoesters and that it occurs within a few hours after administration. The plasma elimination half-life of SMS

and SMP in rats was only a few hours and most of the dose was eliminated after 24 hours. The highest tissue concentrations were reached in the liver, white fat, lung, kidney, spleen and heart. In contrast to SMP, SMS showed a dose-proportional retention with the highest levels occurring in the liver. However, the combined retention of SMS and SMP in the liver of rats fed on a diet containing 5% sucrose esters of fatty acids for two years was less than 0.1%. Thus, there seems to be no time dependent accumulation of sucrose monoesters in the liver. Kinetic studies in humans with S-1170 also revealed that only trace amounts of ingested SMS and SMP were detectable in plasma a few hours after administration. As in the rat, the plasma SMS levels tended to increase with dose and could still be detected at low levels 24 hours after the last dose.

Two human tolerance studies with sucrose esters of fatty acids (S-1170) are available. In the first study, which had significant deficiencies, most notable in the limited size of the study groups and the lack of controls, it was reported that single doses of 1.5-3 g S-1170, as well as repeated doses of 1-1.5 g three times per day (3-4.5 g/day) for 5-7 days, administered in orange juice and bread, were associated with laxation and related abdominal symptoms. A divided dose of 2 g per day for 5 days, equal to 33 mg/kg bw/day, produced no effect when administered in orange juice, and only a slight effect in 1/5 persons when administered with bread. The highest dose tested, 4.5 g per day, equal to 75 mg/kg bw/day, produced a range of gastrointestinal symptoms (soft stools, diarrhoea, flatulence, borborygmus and bloated sensation).

The second study employing 10 men and 10 women was well controlled. It used a double-blind, cross-over design and was conducted on an in-patient basis. Subjective symptoms and frequency and appearance of faeces were recorded. Blood pressure, pulse, breathing rate, body temperature, body weight and a standard set of haematological, clinical chemistry and urinalysis parameters were recorded prior to administration of the test substance and after the end of the treatment periods at day 7. Divided daily doses in bread of 1.5 g for 5 days (equal to 27 mg/kg in men and 29 mg/kg in women) produced no adverse reactions. However, this was the only dose level tested, and it was lower than the dose range (33 – 75 mg/kg bw/day) reported to produce symptoms of laxation in the first study.

These human studies suggest that ingestion of amounts above around 2 g/day in adults might give rise to gastrointestinal symptoms.

CONCLUSIONS AND RECOMMENDATIONS

Sucrose esters of fatty acids have a low oral toxicity and do not raise concern of carcinogenicity. Metabolic studies *in vitro* and in rats, dogs and humans show that these esters are extensively hydrolysed in the gastrointestinal tract into well-known food constituents prior to absorption, that only small amounts of intact monoesters which escape hydrolysis are absorbed, and that incompletely hydrolysed sucrose esters appear to be excreted in the faeces. Studies using radiolabelled sucrose esters indicate that it is unlikely that di- and higher esters

are absorbed intact. There was no evidence of tissue accumulation of the absorbed monoesters that were completely metabolised to carbon dioxide or integrated into other endogenous constituents.

From the new 2-year chronic toxicity/carcinogenicity study a NOAEL can be established at 5% sucrose esters of fatty acids in the diet of rats, equal to 1970 mg/kg bw/day in males. The sucrose esters of fatty acids tested was composed of sucrose esters of stearic and palmitic acids (70:30) with a high content of tetra- and higher esters. The main effects seen in rats in previous long-term studies on sucrose esters of fatty acids containing lower levels of higher esters at very high doses ($\geq 10\%$ dietary levels) were a tendency towards lower body weights, soft stool and diarrhoea. The NOAEL of 2000 mg/kg bw/day from the new long-term rat study can now be established.

Concern about a potential laxative effect in humans was raised by results from an inadequate study in which laxation and related abdominal symptoms were reported in humans ingesting doses of sucrose esters of fatty acids exceeding 2g/day equivalent to 33 mg/kg bw/day. In a subsequent well designed and conducted human tolerance study no adverse effects were observed in men and women receiving divided daily doses of 1.5 g sucrose esters of fatty acids in bread for 5 days (equal to 27 mg/kg in men and 29 mg/kg in women). However, this was the only dose level tested, and it was lower than the dose range (33 – 75 mg/kg bw/day) reported to produce gastrointestinal symptoms in the first study.

Considering all the toxicity data with an overall NOAEL of 2000 mg/kg bw/day a group ADI of 40 mg/kg bw/day can be established for sucrose esters of fatty acids (E 473) and sucroglycerides (E 474). However, in view of the human tolerance studies the Panel wishes to point out that at daily doses above 2 g/day in adults these substances may cause gastrointestinal symptoms. This ADI covers products containing mono-, di- and triesters with a content of tetra and higher esters of no more than 10%.

Conservative estimates of chronic intake of sucrose ester of fatty acids (E 473) and sucroglycerides (E 474) in the adult population were above 20 mg/kg bw/day at the 95th percentile. In young children, conservative estimates of the chronic intake approach the ADI. Refined chronic intake estimates are needed. Based on current Maximum Permitted Levels, for a variety of foods and beverages, a single eating occasion would lead to intakes of sucrose esters of fatty acids (E 473) and sucroglycerides (E 474) in the range of 1 g. High intakes on a one day basis could therefore be expected, particularly in children.

DOCUMENTATION PROVIDED TO EFSA

The dossier submitted by the applicant contained summary tables of previously submitted toxicological data on sucrose esters of fatty acids, and new studies on the absorption, distribution, metabolism and excretion (ADME) of sucrose esters of fatty acids in rodents,

dogs and humans, a 13-week toxicity study in rats, a two-year combined chronic feeding and carcinogenicity study in rats, and a laxative study in human healthy volunteers.

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APPENDIX

Toxicological data on sucrose esters of fatty acids generated prior to the SCF evaluation in 1992 (SCF 1992)

Species (no per group) and study duration	Test sample	Dosages	NOAEL	Observed effects	Reference
Dog (6) 2 years	Sucrose monopalmitate	0, 0.3, 1, and 3% in the diet	3% in the diet	No treatment related toxic effects	Paynter & Crews (1966) WHO (1976)
Rat (30) 18 months	Sucrose esters of tallow	0, 0.3, 1, and 3% in the diet	3% in the diet	No treatment related toxic effects	Kotani (1974) WHO (1980)
Rat (30) 14 months	Sucrose esters of tallow	0, 0.5, 1, and 3% in the diet	0.5% in the diet	2 week period of temporary body weight reduction	Oshima & Kajawara (1960) WHO (1976)
Dog (10) 132 weeks + 8 weeks reversal	Palm oil sucroglycerides (50% sucrose esters)	0, 5, 10, and 20% sucroglycerides in the diet	5% sucrose esters (10% sucroglycerides)	At highest dose: reduced body weight (reversible), increased relative kidney weight (reversible), fat deposits in livers of female	Chesterman (1980) WHO (1990)
Rat (9-11) 24-28 months	Sucrose esters of lard	5 and 10% in diet. Control 3.6% lard in the diet	10% in diet	No treatment related toxic effects	Tudisco & Chiancone (1965) WHO (1976)
Rat (12 males) 25-28 months	Sucrose esters of palm oil	0 and 10% in the diet	10% in diet	No treatment related toxic effects	Tudisco & Chiancone (1965) WHO (1976)
Rat (30) 14 months	Sucrose esters of palm oil	0 and 0.5% in the diet	0.5% in the diet	No treatment related toxic effects	Chiancone (1963) WHO (1976)
Rat (50) 2 years	Sucrose monopalmitate	0, 0.3, 1, 3% in the diet	3% in the diet	Periods of reduced body weight, food consumption and feeding efficiency at 3% in the diet	Paynter (1966) WHO (1976)
Mouse (42)	Sucrose esters	0, 0.3, 3% in	3% in the diet	No treatment	Murata

Sucrose esters of fatty acids, E 473 and sucroglycerides, E 474

Species (no per group) and study duration	Test sample	Dosages	NOAEL	Observed effects	Reference
19 months	of stearic and palmitic acids	the diet		related toxic effects	(1976) WHO (1976)
Rat (30) 2 years parent generation, 21 months F1 generation, and 14 months F2 generation	Sucrose esters of palm oil	0 and 5 g/kg bw/day	5 g/kg bw/day	No treatment related toxic effects	Mosinger (1964) WHO (1976)
Rat (100) 2 years	Palm oil sucroglycerides	0, 5, 10 and 20% in the diet	10% (5% SE) in the diet	Reduced bw gain, changes in organ weight and histopathology at the highest dose	Hunter (1982) WHO (1990)
Rat (24) 22 months parent generation, 21 months F1 generation, and 14 months F2 generation	Sucrose monopalmitate	0, 1% in the diet	1% in the diet	No treatment related toxic effects	Paynter (1965) WHO (1976)
Rat (30) 2 years (2 generation reproduction)	Sucrose esters of lard	0, 5 g/kg bw/day	5 g/kg bw/day	No treatment related toxic effects	Mosinger (1964) WHO (1976)
Rat (10) 100 days	Sucrose monopalmitate	0, 1, 2, 3, 5, 10, and 25% in the diet	3% in the diet	Animals developed diarrhoea and died at the higher doses	Tudisco (1961) WHO (1976)
Rat (?) 60 days	Sucrose monopalmitate & monostearate	100, 200, 1000, and 2000 mg/kg bw/day	2000 mg/kg bw/day	No effects on growth or organ weights	Hara (1959) WHO (1976)
Rat (?)	Sucrose	0, 2, 5, 10, and	10% in the diet	Growth	Oshima &

Sucrose esters of fatty acids, E 473 and sucroglycerides, E 474

Species (no per group) and study duration	Test sample	Dosages	NOAEL	Observed effects	Reference
6 months	monooleate	20% in the diet		reduction at 20%, reversible during recovery phase. Initial diarrhoea at 10 and 20% in the diet, but animals recovered	Kajiwara (1960) WHO (1976)
Rat (16) 100 days	Sucrose esters of palm oil	0, 3, 5, and 10% in the diet	10% in the diet	No treatment related toxic effects	Balea (1963) WHO (1976)
Rat (8-10) 100 days	Sucrose esters of palm oil	0, 5, and 10% in the diet	10% in the diet	No treatment related toxic effects	Tudisco (1963) WHO (1976)
Rat (10) 3.5 month + 1 generation reproduction	Sucrose esters of palm oil	0 and 2% in the diet	2% in the diet	No treatment related toxic effects	Ferrando (1964) WHO (1976)
Rat (?) 200 days	Sucrose esters of lard	25% SE in the diet, controls 18% lard + 7% sucrose	25% in the diet	No treatment related toxic effects	Tudisco (1967) WHO (1976)
Rat (6) 26 weeks	Sucrose esters of palmitic & stearic acids	0, 0.3, 1, and 3% in the diet	3% in the diet	No treatment related toxic effects	Chesterman (1979) WHO (1980)
Dog (8) 26 weeks	Sucrose esters of tallow	0, 0.3, 1, and 3% in the diet	3% in the diet	No treatment related toxic effects	Virgo (1979) WHO (1980)
Human tolerance (?)	Sucrose esters of lard	Up to 100 g/day		No effect on excreted fat or plasma turbidity	Berry & Turner (1960) WHO (1976)
Human tolerance and metabolism (?)	Sucrose esters of tallow	1 g and 10 g		Digestion was rapid and almost complete	Daniel (1979) WHO (1990)