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FOOD ADDITIVE SAFETY

Dr. Alan Rulis
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, Maryland 20740-3835

Re: GRAS Notification for Sucrose Fatty Acid Esters

Dear Dr. Rulis:

Pursuant to proposed 21 C.F.R. § 170.36(c) and on behalf of our client, Mitsubishi Chemical Corporation of Tokyo, Japan, we hereby notify the agency of our determination on the basis of scientific procedures that sucrose esters of fatty acids are generally recognized as safe (GRAS) when used as an emulsifier in certain carotenoid color preparations. As with all GRAS substances, sucrose esters of fatty acids when used in this application are exempt from the premarket clearance requirement applicable to food additives under section 409 of the Food, Drug, and Cosmetic Act.

An earlier version of this GRAS Notification was submitted to the agency in December, 2001, and designated GRAS Notification No. 92. In a letter dated February 4, 2002, the agency explained its view that GRN 92 did not provide a sufficient basis for a determination that sucrose fatty acid esters are GRAS under the described conditions of use. The present submission includes additional information supporting the GRAS determination.

More specifically, the Agency raised three issues in its letter of February 4, 2002: (1) that a two-year rat feeding study relied upon in support of the GRAS determination did not yet appear in print; (2) that a time-gap would be appropriate following publication of that study before GRAS status is claimed; and (3) GRAS status may require that more published safety data, beyond the two-year rat feeding study, be publicly available. The first and second points raised by the agency have been made moot by publication of the two-year rat feeding study in April, 2002, and the passage of time since then. The third point is addressed by reliance upon a larger body of published studies in the present submission.

In terms of published data, this submission relies primarily upon (1) the now-published 90-day and two-year rat feeding studies (Takeda and Flood, 2002); (2) metabolism studies in rats of sucrose esters of stearic acid and palmitic acid using esters labeled with ^{14}C at the sucrose or fatty acid moiety - showing that sucrose esters are hydrolyzed to sucrose and fatty acids prior to absorption (Shigeoka *et al.*, 1984); (3) metabolism studies in rats using tetra-, hexa-, and octa-stearic acid esters of sucrose when administered by oral gavage (Noker *et al.* 1997).

Most importantly, the published studies include the two-year and 90-day rat feeding studies, from which an adequate no-observed-adverse-effect level (NOAEL) can be derived. The body of published data also includes metabolism studies demonstrating that sucrose esters of fatty acids are not likely to be absorbed intact. To the extent that they are absorbed at all, they are likely to be hydrolyzed first into free sucrose and edible fatty acids, which are normally present in the diet. This body of published safety data forms a sufficient basis for a GRAS determination by qualified experts and is further supported by unpublished corroborative data.

In its letter of February 4, 2002, FDA noted that a human tolerance study of sucrose esters reviewed by the Joint (FAO/WHO) Expert Committee on Food Additives (JECFA) is not published. This study confirmed that sucrose esters will not cause laxation at high doses. Laxation studies are not routinely required during the safety evaluation of food ingredients, and the existence of this unpublished study does not preclude GRAS status. The enclosed GRAS Notification includes a discussion of the estimated daily intake (EDI) associated with sucrose esters and concludes that the EDI associated with uses covered by this submission is approximately 8 mg/person/day. Food safety experts would not be concerned about the possibility of laxation at this low exposure. Furthermore, the human tolerance study reviewed by JECFA and described in JECFA's 1998 toxicological monograph for sucrose esters showed no effects at the highest doses, equal to 27 and 29 mg/kg b.w. in men and women respectively or approximately 1800 mg/person/day. Under these circumstances, the human tolerance study is properly viewed as something that corroborates the safety of sucrose esters but is not pivotal to the safety determination made in the enclosed GRAS Notification.

* * *

In summary, this submission claims GRAS status for sucrose esters of fatty acids when added to the diet at roughly 8 mg/person/day. This use is supported by: a published two-year rat feeding study, a published 90-day rat feeding study, a series of published metabolism studies, a series of JECFA evaluations of sucrose fatty acid esters, and a history of safe use of sucrose fatty acid esters in the United States and around the world dating back more than 20 years. JECFA's acceptable daily intake (ADI) for sucrose fatty acid esters, derived from the published two-year rat feeding study, is 30 mg/kg body weight. This corresponds to 1800 mg/person/day for a 60-kg

adult, which is 225 times higher than the dietary exposure associated with the use described in this Notification.

We trust you will find the enclosed notification acceptable. Should any questions arise during the review process, please do not hesitate to contact us, preferably by telephone, so that we may respond as quickly as possible.

Very truly vours.

John S. Eldred

Enclosure

cc: Ms. Yukino Nagai

GRAS Notification for Sucrose Fatty Acid Esters

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1. Claim regarding GRAS status

Mitsubishi Chemical Corporation hereby notifies the agency through its attorneys of its determination that sucrose fatty acids esters, as defined below, are generally recognized as safe (GRAS) when added to carotenoid color preparations.

As such, sucrose fatty acid esters are exempt from the premarket approval requirements of the Food, Drug, and Cosmetic Act.

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i. Name and address of the notifier

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ii. Common or usual name of the subject substance

The common or usual name of the notified substance is:

Sucrose fatty acid esters

iii. Conditions of use

Sucrose fatty acid esters are intended for use as an emulsifier in carotenoid color preparations. More specifically, this GRAS Notification covers the use of sucrose fatty acid esters (principally the mono-, di-, and tri-esters) in the following three carotenoid colors: β-carotene, β-apo-8'-carotenal (apocarotenal), and canthaxanthin when they are added to the following foods: beverages, crackers, soups, and sauces.

These three carotenoids are permitted color additives, cleared in FDA's regulations at 21 C.F.R. §§ 73.95, 73.90, and 73.75 respectively.

Carotenoid color preparations to which sucrose fatty acid esters are added will contain approximately 10% pure carotenoid and a maximum of 4% sucrose fatty acid ester.

To color many foods with a water-insoluble carotenoid, it is necessary to use an emulsified formulation of the carotenoid. For this purpose, the carotenoid is divided into small particles and dispersed finely in a powder or an aqueous system as an oil-in-water emulsion. The food is then colored by addition of the concentrated carotenoid color preparation.

iv. Basis for the GRAS determination

The GRAS determination for sucrose fatty acid esters is based upon scientific procedures, as described in greater detail in section 3 below.

v. Statement of availability of data and information

The data and information that are the basis for Mitsubishi's GRAS determination are available for review and copying by FDA at the offices of Keller and Heckman, LLP, 1001 G Street, N.W., Washington, D.C. 20001. These documents will be sent to FDA upon request.

2. Detailed Information About the Identity of the Notified Substance

i.	Name:	sucrose fatty acid esters
ii.	Codex INS number:	473
iii.	Physical description:	stiff gels, soft solids, or white to slightly grayish white powders
iv.	Synonyms:	- sucrose esters of fatty acids - sucrose esters - Ryoto Sugar Ester - mono-, di-, and tri-ester of sucrose with edible fatty acids

v. Method of manufacture:

Sucrose fatty acid esters are manufactured by inter-esterification of sucrose with methyl esters of fatty acids. The fatty acids are derived from edible vegetable or hydrogenated edible vegetable oils and fats. They are prepared in the presence of food-grade solvents

such as ethyl acetate, methyl ethyl ketone, dimethyl sulfoxide, or isobutanol, as specified in 21 C.F.R. § 172.859 and the *Food Chemicals Codex*. The ratio of fatty acid methyl ester to sucrose establishes the degree of esterification. The crude reaction product is dissolved in a solvent and then extracted by water to purify.

Sucrose esters can be grouped into three commercial categories: the lower esters (mono-, di- and tri-esters, regulated at 21 C.F.R. § 172.859), the octa-ester also known as olestra (regulated at 21 C.F.R. § 172.867), and the mid-range esters, which are the subject of a pending Food Additive Petition (FAP No. 8A4610). The lower esters meeting the specifications described at 21 C.F.R. § 172.859 are the subject of this GRAS Notification.

vi. Specifications:

Specifications for sucrose fatty acid esters are currently established at 21 C.F.R. § 172.859. Specifications for sucrose fatty acid esters are also included in the first supplement to the 4th Edition of the *Food Chemicals Codex*. Copies of these specifications are presented in Appendix 1 for convenient reference. The sucrose fatty acid esters that are the subject of this Notification meet all relevant specifications of section 172.859 and the *Food Chemicals Codex*.

3. Detailed Summary of Basis for Notifier's GRAS Determination

Mitsubishi's GRAS determination is based upon a series of toxicological studies of sucrose fatty acid esters including most notably published 13-week and 2-year feeding studies conducted in Fischer 344/DuCrj rats. It is also based upon published data and information regarding the metabolic fate of sucrose fatty acid esters in humans.

3.i Subchronic and Chronic Toxicity and Carcinogenicity Studies

A 13-week and a 2-year feeding study were conducted in Fischer 344/DuCrj rats to evaluate the oral toxicity and carcinogenicity of S-570[1], a mixture of mono-, di-, tri-, and higher esters of sucrose with fatty acids derived from edible fats and oils. S-570 was fed at concentrations of 0, 1, 3, or 5% (w/w) of the diet to groups of 20 male and 20 female rats in the 13-week study, and to groups of 50 male and 50 female rats in the chronic toxicity/carcinogenicity study. In the latter study, animals in satellite groups of 14 rats/sex/dose were sacrificed at 12 months to evaluate chronic toxicity.

[1] S-570 is the commercial designation of a product offered by Mitsubishi. It contains approximately 29% mono-ester, 35% di-ester, 25% tri-ester, and 11% tetra- and higher esters. 70% of the fatty acid content of S-570 is stearic acid.

Summary of Results of 13-Week Feeding Study

The results of the 13-week study demonstrated that sucrose fatty acid esters were not toxic to rats at doses up to 5% in the diet (equivalent to daily intakes of 3200 - 3400 mg/kg bw). No deaths were noted in any of the groups. Administration of the test material had no consistent effects on body-weight gain, food consumption, or food efficiency. There were no toxicologically significant effects of treatment on the hematological, clinical chemistry, or urinalysis parameters. Slight alterations in some clinical chemistry parameters were observed, but these were minor and within the range observed in control animals. Other statistically significant observations were not dose-dependent and were not considered related to treatment. A small (less than 3.5%) decease in absolute kidney weight was observed at 3% and 5 % in males but not in females. No macroscopic, organ weight or histopathological changes were observed that could be attributed to treatment (Takada and Flood, 2002; also JECFA 44th Meeting).

Summary of Results of Chronic Toxicity/Carcinogenicity Study

S-570 was administered in the diet to male and female F344/DuCrj rats at concentrations of 0, 1, 3 and 5% in the diet; these concentrations were equivalent to average daily intakes of 0, 394, 1160, and 1970 mg/kg bw in male rats and 0, 480, 1440, and 2440 mg/kg bw in female rats. The study was divided into two parts, a two-year carcinogenicity assay employing 50 rats/sex/group and a one-year chronic toxicity assay in which satellite groups of 14 rats/sex/group were used. Experimental details concerning the diet, animal husbandry, in-life observations, and clinical and pathological observations are thoroughly discussed in Takeda and Flood, 2002.

Survival and weight gain- Treatment with the test material had no effect on survival, and no deaths occurred in the chronic toxicity phase of the study. Body weights of the male rats receiving the 5% dose were lower than controls at various points during the first year of the study; the weight decrements were only 2-3%. Food consumption was clearly lower in the first few weeks of administration in males of the high-dose group and sporadically thereafter. Small, sporadic, but statistically significant, differences between test and control weight gains occurred in females, but these could not be related to treatment.

Hematology and clinical chemistry- Statistically significant increases in mean corpuscular volume (MCV) affecting mainly the high-dose animals were noted at many of the sampling points. Sporadic decreases in red blood cell (RBC) count, hemoglobin concentration, mean corpuscular hemoglobin concentration (MCHC), and platelet count were also noted particularly toward the end of the study. In all cases, these differences were small, were not consistently seen throughout the study, and were within the normal range of values found for this strain of rat. They were therefore judged to be of no toxicological significance.

Organ weights- No significant differences in organ weights from those in the controls were observed at week 52 in the satellite groups. At 104 weeks, absolute and relative spleen weights were higher than controls in males from the 3 and 5% dose groups. In females, significant increases in absolute and relative spleen weight and absolute lung weight were observed in the 3% dose groups but not in the 5% group. The spleen weight changes were likely due to the incidence of large granular lymphocyte (LGL) leukemia. This was a commonly occurring neoplasm in all groups and was slightly increased, without statistical significance, at the two top doses in both sexes. Historical control incidences of LGL leukemia as high as 24% in males and 25% in female F344 rats have been noted in the laboratory conducting the study. Incidences in this study varied from 14% to 28%. The highest incidence occurred in females in the 3% treatment group, with a lower incidence in the 5% group. Consequently, LGL leukemia and its sequalae (spleen enlargement, haematopoiesis in the spleen and haematopoeitic hyperplasia) were not considered related to treatment. When leukemic animals were removed from spleen weight determinations, no treatment-related differences were apparent.

Histology – Microscopic examination of tissues showed no significant difference between treated and control animals related to the test substance. There were no lesions in the GI tissues, mesenteric lymph nodes, or liver. A slight increase in extramedullary hematopoiesis (EMH) was observed in the spleen in the animals sacrificed after 104 weeks. These incidences were not statistically significant. A slight increase in LGL leukemia was observed in both sexes, but the increases were not statistically significant and as indicated above were not unexpected given the high historical incidence of these lesions in this strain of rat.

ADI Calculation- No adverse effects of treatment were demonstrated in the long-term toxicity/carcinogenicity study conducted in rats at doses up to 5% in the diet, equivalent to 1970 mg/kg bw/day in males and 2440 mg/kg bw/day in females. The ADI based on this study is 19.7 mg/kg bw/day using the lower NOAEL calculated for male rats and the traditional 100-fold safety factor for a chronic study.

At its 44th meeting, JECFA established an ADI of 0-20 mg/kg bw for the sucrose fatty acid esters on the basis of this study. At its 49th meeting, JECFA revised the ADI upwards, accepting that a safety factor of only 50, rather than 100, can be used to derive an ADI from this particular study. According to JECFA, "the lower safety factor was considered appropriate for sucrose esters of fatty acids since these compounds are hydrolysed to normal dietary constituents in the gastrointestinal tract prior to absorption." A straightforward application of the 50-fold safety factor would have yielded an ADI of approximately 40 mg/kg bw. However, because the potential of sucrose esters to induce laxation at this high a dose (2.4 grams per day for a 60-kg adult) could not be excluded, JECFA capped the ADI at 30 mg/kg bw, which corresponds to the highest dose and the no-effect-level in a human tolerance study reviewed by JECFA and described in JECFA's 1998 toxicological monograph for "Sucrose Esters of Fatty Acids and Sucroglycerides" (Appendix 6.H). A more complete discussion of JECFA's evaluations of sucrose esters is presented in Appendix 6.

FDA has evaluated the above-described safety study in the course of reviewing pending Food Additive Petition No. 8A4610. That Petition seeks clearance for the mid-range sucrose esters (average degree of esterification ranging from four to seven) when added to low-fat spreads and chocolate. The Petition is expected to be granted soon.

3.ii <u>*Metabolic and Pharmacokinetic Data*</u>

Introduction - Metabolic and pharmacokinetic data (ADME) are informative, but usually not dispositive, in judging the safety of a substance added to food. As long as the essential toxicological studies with adequate NOELs are available, the metabolic data can provide additional insights with regard to mechanism, but they are typically insufficient *per se* to determine safety. Questions can remain concerning the toxicity of the parent or the metabolites whatever their dose, distribution, or elimination patterns. But, when the substance can be shown to be excreted unchanged or metabolized solely into constituents that are safely consumed as food, or the same as those formed from food, metabolic information takes on greater weight. This is true in the case of sucrose fatty acid esters.

What follows is a general description of what is known about the absorption, distribution, and metabolism of sucrose esters, and then a summary of the studies from which this understanding is derived.

The *in vivo* pharmacokinetic data (Noker *et al.*, 1997) and *in vitro* absorption studies (Shigeoka *et al.*, 1984) demonstrate that virtually no intact sucrose fatty acid esters are absorbed as such, except for a small amount (0.33%) of monoester (Hirano *et al.*, 1994). The higher esters (di-, tri-, tetra-, and higher) are absorbed only after hydrolysis to sucrose and fatty acids. The extent of this hydrolysis depends on the degree of esterification of the sucrose ester. It is well-accepted that the higher esters of sucrose with fatty acids, the octa-esters and hepta-esters present in the fat substitute *Olestra*, are not absorbed by humans and are excreted unchanged (61 *Fed. Reg.* 3118).[2] The lower esters are partially hydrolyzed and, as stated above, are to that extent absorbed as sucrose and individual fatty acids. More specifically, some amount of the di-, tri-, and tetra-esters is excreted unchanged and some amount is hydrolyzed or partially hydrolyzed to form edible fatty acids, free sucrose, and/or sucrose esters with a lower degree of esterification (*e.g.*, the tri-ester is hydrolyzed to form the di-ester and a free fatty acid).

Metabolism of the sucrose fatty acid esters - Early studies on the metabolism of sucrose monoesters: sucrose monostearate, monopalmitate, monooleate and others (Berry and Turner, 1960) demonstrated that the esters were enzymatically converted to sucrose and to fatty acids via pancreatic lipase similar to the conversion of triglycerides into glycerol and fatty acids. By contrast, Mattson and Nolen (1972) demonstrated that pancreatic lipase did not hydrolyze fatty acid esters that contained more than three ester groups. Instead, less efficient enzyme systems were activated for these higher esters, and even

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[2] 61 *Fed. Reg.* 3118 (Jan. 30, 1996 promulgation of food additive regulation for Olestra, 21 C.F.R. § 172.867). See, 61 *Fed. Reg.* 3118 at 3125-3127.

these did not cleave compounds containing more than five ester groups. As a result, as the number of ester groups increased in the molecule, its absorbability decreased.

Daniel *et al.* (1979) studied the metabolism of sucrose mono- and di- esters of beef tallow in rats and showed that these esters were hydrolyzed to sucrose and fatty acids before absorption and did not accumulate in tissues following repeated exposure. Shigeoka *et al.*, studied the metabolism of sucrose mono-esters of palmitic and stearic acids *in vivo* and *in vitro* using C^{14} labels in both the sucrose and fatty acid moiety. They confirmed that the sucrose esters must be hydrolyzed before absorption by the intestine or transport into the blood system.

ADME data were extended to the higher sucrose esters by Noker *et al.* who studied the tetra-, hexa-, and octa-stearate esters of sucrose. They used a radio-labeled technique similar to Shigeoka *et al.* and could follow the fate of both the sucrose and fatty-acid portions of the molecule. The extent to which each dose was absorbed was determined by measuring radioactivity in expired CO_2, urine, feces, and carcasses 120 hours after dosing. The extent of absorption of the radio-labeled material from the esters was greater for the acid-radiolabeled ester than the sucrose radiolabeled ester. This is consistent with our understanding that the intact ester is hydrolyzed prior to absorption, yielding stearic acid and sucrose moieties to be absorbed at their different rates. To the limits of the method, all of the radioactivity from the hexa- and octa- esters was found in the feces, and at least 98% was present as the intact parent substance. This showed that the higher esters were neither significantly absorbed nor significantly fermented in the large intestine.

These data complete the metabolic picture of the series of sucrose fatty acid esters from the monoester to the octaester. In short, the intact esters are not absorbed as such, with the possible exception of a very small amount of mono-ester. Instead, the esters are hydrolyzed to sucrose and fatty acids and are absorbed as such only following hydrolysis. As the degree of esterification increases, from mono- to octa-, the esters are less easily hydrolyzed, and the extent to which they are absorbed decreases to essentially zero in the case of the octa-ester.

The most significant published studies on the metabolism of sucrose esters are described in greater detail below.

Shigeoka et al., Food and Chem Toxicol 22:409-414 (1984) (Appendix 3)

The metabolism in rats of sucrose ester of stearic acid and palmitic acid was studied *in vivo* and *in vitro* using esters labeled with ^{14}C at the sucrose or fatty acid moiety. In the *in vivo* studies, the ratio of expired radioactivity to absorbed radioactivity after oral administration of the sucrose esters labeled at the sucrose moiety was similar to that after the administration of [^{14}C]sucrose. A similar correlation between the ester labeled at the fatty acid moiety and the free [^{14}C]fatty acid was also observed. This suggests that the sucrose esters were hydrolyzed to free fatty acids and sucrose prior to absorption. No intact sucrose ester was detected in the urine.

Studies *in vitro* using everted intestinal sacs showed that there was virtually no transport of ^{14}C-labeled sucrose esters (intact ester) from the mucosal to the serosal solution through the intestinal tissues, and that the enzymes in the intestinal mucosa played a more important role in the hydrolysis of sucrose esters than did those in the digestive fluid. In studies of intestinal absorption through the mesenteric lymphatic system, during the 24 hours after ingestion, 1.8% of the administered radioactivity was recovered in the lymph after dosing with [^{14}C]sucrose monostearate (^{14}C-labeled on the sucrose portion of the molecule) whereas 20% was recovered in the lymph after dosing with sucrose [^{14}C]monostearate (^{14}C-labeled on the fatty-acid portion of the molecule). This difference in recovery in lymph of administered radioactivity indicated that sucrose monostearate was absorbed only after hydrolysis, *i.e.,* the rates of recovery reflect the relative rates at which free sucrose and stearic acid are absorbed and transported to the lymph. No intact ester was detected in the lymph or in the portal or femoral blood.

Noker et al. . Food and Chem Toxicol 35:589-595 (1997) (Appendix 4)

This study reports on the metabolism of tetra-, hexa-, and octa- stearic acid esters of sucrose when administered by oral gavage. Note that these test substances have a degree of esterification (tetra-, hexa-, octa-) that extends somewhat beyond the scope of this GRAS Notification. This information is included, however, because it assists in the overall understanding of the metabolism of sucrose esters. The ^{14}C labels were placed in either the sucrose (uniformly labeled) or the in the fatty acid (alpha position) portions of the molecule. The Table below shows the major results.

Excretion of radioactivity during 120 hours following gavage administration of sucrose esters

% Dose Recovered in:

Compound		CO_2	Urine	Cage Rinse	Feces	Carcass	% of dose Absorbed**	Ratio CO_2/ Absorbed***
Acid Label	tetra	1.6	0.3	0.4	99.2 (4.7)*	4.1	5.9	0.28
	hexa	0.8	0.1	0.1	111 (1)	1.6	2.5	0.30
	octa	0.5	0.1	0.1	115 (2)	1.8	2.4	0.22
Sucrose Label	tetra	1.5	1.0	0.3	96 (17)	0.5	3.0	0.52
	hexa	0.3	0.4	0.0	108 (6)	0.2	0.8	0.43
	octa	0.3	0.5	0.01	112 (5)	0.2	0.8	0.38

* The numbers in parenthesis are SD's for three rats.

** The sum of radioactivity in expired CO_2, urine, and carcass [as reported, presumably with rounding].

*** % of dose recovered in CO_2 divided by the % of dose absorbed.

The data show the following:

(1) The degree of absorption as calculated from the cumulative collections of expired CO_2 and urine and the amount of radioactivity in the carcasses was highest for the tetra-ester regardless of the position of the label. TLC analyses of feces collected from rats administered the tetra-ester showed that 88.2 ± (6.5)% of the extractable radioactivity in feces represented the parent compound. The tetra-ester was hydrolyzed to absorbable radioactivity slowly, but more readily than the higher esters. (The bioavailability of the tetra-ester was not determined, but radioactivity in the blood became detectable within 1-4 hrs after dosing and was slowly eliminated.)

(2) The extent of absorption of the radio-labeled material from the esters was greater for the acid-radiolabeled ester than the sucrose radiolabeled ester. This is consistent with the findings of Shigeoka *et al.,* and our belief that the intact ester is hydrolyzed prior to absorption, yielding stearic acid and sucrose moieties to be absorbed at their different rates.

(3) A greater percentage of the absorbed dose was converted to CO_2 following dosing with the sucrose-labeled esters than with the fatty acid –labeled esters. Apparently once sucrose is liberated, it is more readily oxidized into CO_2 than is stearic acid.

(4) In a separate study rats were subjected to thoracic duct cannulation, and lymph was collected from dosed animals continuously for up to 120 hours after dosing. On TLC analysis of lymph samples, no intact parent compound was detected. While more radiolabel in lymph was measured for the tetra-esters (tetra =5.0-7.6%; hexa = 0.5 –2.8%; octa = 1.2 -1.6%), in no instance was any intact ester found.

(5) The lymph collection study showed that no intact parent compounds could be identified, although in lymph samples collected for up to 120 hours from the thoracic duct following administration of [^{14}C- fatty-acid-labeled] tetra-, hexa-, or octa-esters, 0.5 to 7.6% of the dose was present. For up to 96 hours following administration of [^{14}C-sucrose-labeled] tetra-, hexa-, or octa-esters, less than 0.3% of the dose was present. These data indicate that a different radioactive species was absorbed following administration of ^{14}C- fatty-acid-labeled esters than following administration of ^{14}C-sucrose-labeled esters. This could occur only if the compounds were metabolized during or prior to absorption, yielding ^{14}C-labeled stearic acid and ^{14}C-labeled sucrose as the radioactive moieties.

Once again, the overall picture derived from these studies is the intact esters are not absorbed as such, with the possible exception of a very small amount of mono-ester. Instead, the esters are hydrolyzed to sucrose and fatty acids and are absorbed as such only following hydrolysis.

Fate and properties of the higher esters - The sucrose fatty acid esters covered by this Notification contain some amount of tetra- and higher esters, ranging from close to zero to 10% and higher. As indicated above, it is expected that there will be no appreciable absorption of this fraction of the sucrose fatty acid esters and it will remain unabsorbed in its transit through the digestive system. It is reasonable to ask whether this unabsorbed material can exert any adverse influence either itself in its passage through the body, e.g., an effect on laxation, or indirectly, by a sequestration of fat-soluble vitamins. Both these concerns were taken into consideration in the FDA's clearance of olestra, which is defined to contain at least 70% of the octa-ester. Olestra is approved for use in savory snacks without limitation except for GMPs, and intakes of a few grams per day are anticipated (21 CFR § 172.867). Olestra is required to be supplemented with μg/g levels of several vitamins to compensate for possible interference with vitamin absorption. But, in the present instance, it is obvious from the intake of sucrose fatty acid esters expected, (about 8 milligrams/person/day as shown in section 3.vi below, compared to 7 grams/person/day in the case of Olestra (61 *Fed. Reg.* 3124)), that these concerns are non-existent. There is no conceivable way such a small quantity of unabsorbed lipid-soluble material could influence laxation or affect vitamin absorption. The possibility of laxation is further resolved by the most recent human tolerance study examined by JECFA, which is described in Appendix 6.A and in JECFA's most recent toxicological monograph for sucrose esters (Appendix 6.H).

3.iii <u>*JECFA Evaluations*</u>

The Joint (FAO/WHO) Expert Committee on Food Additives (JECFA) has evaluated the safety of sucrose fatty acid esters (the lower esters, principally mono-, di-, and tri-esters) on eight occasions, producing seven toxicological monographs. We are including this information because JECFA's pronouncements on the safety of sucrose esters helps to establish the expert consensus needed for GRAS status. JECFA's toxicological monographs for sucrose esters are presented as appendices to this submission. For the Agency's convenience, and because this information is voluminous, we have prepared our own summary of JECFA's evaluations, which is presented in Appendix 6

Most concisely, JECFA has determined that the acceptable daily intake for sucrose esters is 30 mg/kg body weight. For a 60-kg adult, this corresponds to 1800 mg/person/day, a level that is 225 times the estimated daily intake associated with the use of sucrose esters in carotenoid color preparations when added to foods, as covered by this Notification. (See intake estimate presented on pages 11 - 14.)

3.iv <u>*Other Safety Information*</u>

Sucrose esters have been permitted and used in foods as emulsifiers for many years in Japan, Europe, and North America. As noted above, sucrose esters can be grouped into three commercial categories: the lower esters (mono-, di- and tri-esters, regulated at 21

C.F.R. § 172.859), the octa-ester also known as olestra (regulated at 21 C.F.R. § 172.867), and the mid-range esters, which are the subject of a pending Food Additive Petition (FAP No. 8A4610), which is expected to be granted soon. The lower esters meeting the specifications described at 21 C.F.R. § 172.859 are the subject of this GRAS Notification.

To support our determination of GRAS status in this particular application, we rely primarily upon the recently published 90-day and two-year rat feeding studies described above. We also cite other relevant information including FDA's own informal acceptable daily intake (ADI) for sucrose esters of fatty acids, 25 mg/kg body weight per day and evaluations by the Joint (FAO/WHO) Expert Committee on Food Additives.

In 1993, in the context of evaluating three Food Additive Petitions seeking to expand the permitted uses for sucrose esters under section 172.859, FDA revised its ADI for the lower sucrose esters. The agency's conclusions are embodied in a memorandum dated November 4, 1993, which is presented as Appendix 5. FDA assigned an ADI of 25 mg/kg b.w. to sucrose esters, expressed as 1500 mg/p/day for a 60-kg adult. We do not cite this as freestanding evidence that sucrose esters qualify as GRAS, but it certainly represents a publicly-available safety opinion rendered by qualified experts.

3.v *Safety Determination*

As shown in section 3.vi below, the intake of sucrose esters associated with their use in carotenoid color preparations is no more than 8 mg/person/day, or roughly 0.13 mg/kg body weight for a 60-kg adult. This intake estimate represents a trivial incremental exposure relative to the ADI for sucrose esters and existing potential exposure. More specifically, 0.13 mg/kg b.w. is approximately 200 times lower than FDA's own ADI for sucrose esters, 25 mg/kg b.w.

The existing body of safety data is more than adequate to support a determination that sucrose esters are safe at this incremental additional level of exposure.

3.vi *Intake Estimate*

The intake of sucrose esters associated with their use in carotenoid color preparations will be a small fraction of the acceptable daily intake (ADI) established by FDA, JECFA, and other expert bodies.

Sucrose esters will be used at a maximum level of 4% in the carotenoid color preparations, which will be added to beverages, crackers, soups, and sauces for the purpose of imparting orange/yellow/red hues characteristic of the carotenoids. The intake of sucrose fatty acid esters associated with this use can be estimated as follows.

Food Type	Typical Concentration of pure carotenoid in the food	Corresponding Sucrose Ester concentration in the food (maximum)[3]	Daily consumption of the food	Daily consumption of sucrose esters
Beverages[4]	β-carotene: 30 ppm	12 ppm	600 ml (g)	**7.2 mg**
	Apocaroenal: 12.5 ppm	5 ppm	600 ml (g)	3 mg
	Canthaxanthin: 29.1 ppm	11.6 ppm	600 ml (g)	7 mg
Crackers	β-carotene: 20 ppm	8 ppm	23 g[5]	**0.2 mg**
	Apocaroenal: 20 ppm	8 ppm	23 g	0.2 mg
	Canthaxanthin: 20 ppm	8 ppm	23 g	0.2 mg
Soups	β-carotene· 1.3 ppm	0.5 ppm	245 g[6]	**0.1 mg**
	Apocaroenal: 1.3 ppm	0.5 ppm	245 g	0.1 mg
	Canthaxanthin: 1.3 ppm	0.5 ppm	245 g	0.1 mg
Sauces	β-carotene: 12 ppm	4.8 ppm	125 g[7]	**0.6 mg**
	Apocaroenal: 12 ppm	4.8 pm	125 g	0.6 mg
	Canthaxanthin: 12 ppm	4.8 ppm	125 g	0.6 mg
Total				**8.1 mg**

[3] The carotenoid color preparations will typically contain 10% pure carotenoid and a maximum of 4% sucrose fatty acid esters. This means the ratio of sucrose ester to pure carotenoid is 0.4 to 1.

[4] Beverages to which carotenoid colors may be added include carbonated soft drinks, sugar-free carbonated soft drinks, non-carbonated soft drinks, and fruit ades. According to published USDA survey data (Foods Commonly Eaten by Individuals: Amount Per Day and Per Eating Occasion, Home Economics Research Report No. 44, March, 1982), the quantity of these beverages consumed per day by users who reported consumption at least once during a three-day period ranged as high as 556 g/day at the 90th percentile level (for carbonated soft drinks). Because a single individual is unlikely to consume all four beverage categories at the 90th percentile level, we take 600 g/day to approximate the level at which carotenoid-containing beverages might be consumed by heavy consumers of these products.

[5] Foods Commonly Eaten by Individuals: Amount Per Day and Per Eating Occasion, Home Economics Research Report No. 44, March, 1982. 23 g/day represents the daily consumption at the 90th percentile level among consumers who reported consumption of crackers at least once during a three-day period.

[6] Foods Commonly Eaten by Individuals: Amount Per Day and Per Eating Occasion, Home Economics Research Report No. 44, March, 1982. 245 g/day represents the daily consumption at the 90th percentile level among consumers who reported consumption of soup at least once during a three-day period.

[7] Daily consumption of sauces is not reported in the above-referenced USDA survey data. The figure we are using, 125 g/person/day, is taken from FDA's nutrition labeling regulations, § 101.12, Reference amounts customarily consumed per eating occasion, Table 1. Amount consumed per eating occasion is obviously not the same thing as daily consumption at the 90th percentile level, but we believe this figure represents an exaggerated estimate, as an individual is unlikely to consume sauces every day.

A single food will not contain more than one added carotenoid color. In other words, if a beverage is colored with β-carotene, it will not also contain apocarotenal or canthaxanthin. Therefore, in evaluating the cumulative EDI associated with the uses described above, we have counted only the maximum level at which sucrose esters may be present in each food category.

Thus, the cumulative EDI associated with the use of sucrose esters in the three carotenoid colors, when these colors are added to beverages, crackers, soups, and sauces, is approximately **8 mg/person/day**.

Cumulative Exposure

In addition to assessing the EDI for sucrose esters associated with the uses covered by this GRAS Notification, we have considered the cumulative dietary intake of sucrose esters associated with their use in other foods. Sucrose esters are cleared for a variety of uses at 21 C.F.R. § 172.859. In evaluating the cumulative EDI associated with these uses, it is appropriate to consider the entire market for emulsifiers and the market share attributable to sucrose esters.

According to the most recent (1987) National Academy of Sciences survey of food additive usage, the total volume of emulsifiers added to the diet that year was 71 million pounds. FDA sometimes applies a factor of 0.6 to data collected in the poundage survey to account for under-reporting. This would increase the total volume of emulsifiers believed to have been added to the U.S. diet in 1987 to 118 million pounds. Based upon the U.S. population in 1987 of 243 million, *per capita* emulsifier exposure was 600 mg/person/day. The total poundage of emulsifiers added to the diet since 1987 has undoubtedly increased along with the U.S. population. However, because the market for emulsifiers was mature in 1987, there is no reason to expect the *per capita* exposure to emulsifiers to have increased significantly since 1987.

In the unlikely event that sucrose esters captured 100% of the emulsifier market in the United States, the resulting *per capita* exposure would be 600 mg/person/day, as calculated above. This figure is well within the agency's ADI for sucrose esters, 25 mg/kg body weight per day (1500 mg/person/day for a 60-kg adult or 625 mg/person/day for a 25-kg child).

A more realistic scenario is that sucrose esters will capture no more than 10% of the emulsifier market in the United States, considering the large number of emulsifiers that are available (43 reported in the 1987 poundage survey) and considering that the market in 1987 was dominated by mono- and diglycerides and lecithin (59% and 18% of the market respectively). If sucrose esters were to capture 10% of the emulsifier market, *per capita* dietary exposure to sucrose esters would be approximately 60 mg/person/day according to the above analysis. Because emulsifiers are ubiquitous and evenly distributed throughout the food supply, we can reasonably expect that most consumers will not exceed the *per capita* exposure estimate, particularly on a long-term basis.

However, a particular consumer would need to exceed this *per capita* exposure estimate by a factor of 25 to exceed the ADI for sucrose esters (1500 mg/person/day for a 60-kg adult), and this is extremely unlikely.

A higher cumulative intake estimate would be obtained if we considered each food category for which sucrose esters are presently authorized and evaluated the daily consumption of those foods together with typical levels of use for sucrose esters. This approach, however, would lead to a gross over-estimation of actual consumer exposure because it would be based upon an unreasonable assumption that all baked goods, frozen dairy desserts, etc., contain emulsifiers and that the only emulsifier used in these foods is sucrose esters.

3.vii *Expert Consensus*

The use of sucrose esters of fatty acids in a variety of food applications is widely known and recognized as safe among qualified experts around the world.

The article presented as Appendix 2 reporting on 90-day and two-year rat feeding studies has been published in a peer-reviewed scientific journal. Included with Appendix 2 is a copy of this article. The key metabolic and pharmacokinetic data, which in this instance are highly relevant to the safety assessment, also are published in peer-reviewed journals.

As indicated above, a monograph for sucrose fatty acid esters appears in the First Supplement to the Fourth Edition of the *Food Chemicals Codex*. The FCC identifies functional use categories for sucrose esters as emulsifier, stabilizer, and texturizer.

As also noted above, JECFA has evaluated sucrose esters of fatty acids numerous times and has assigned a group ADI of 30 mg/kg b.w. to the sucrose ester content of sucrose esters of fatty acids and sucroglycerides.

All of these facts taken together support a conclusion that sucrose esters of fatty acids are GRAS in the application described in this Notification. More specifically, the requirement that the pivotal underlying safety data be ordinarily published is satisfied by publication of the 90-day and two-year S-570 feeding studies in a peer-reviewed scientific journal, along with other published data. The requirement that qualified experts agree on the safety of sucrose fatty acid esters is met in several ways including the agreement exhibited by the authors and peer reviewers of the published S-570 study and favorable conclusions of JECFA, FDA, and regulatory bodies around the world regarding sucrose esters of fatty acids.

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61 *Fed. Reg.* 3118 (Jan. 30, 1996 promulgation of food additive regulation for Olestra, 21 C.F.R. § 172.867).

Appendix 1

Appendix 1: Specifications: 21 C.F.R. 172.859 and *Food Chemicals Codex*

§ 172.856 Propylene glycol mono- and diesters of fats and fatty acids.

Propylene glycol mono- and diesters of fats and fatty acids may be safely used in food, subject to the following prescribed conditions:

(a) They are produced from edible fats and/or fatty acids in compliance with § 172.860 and/or oleic acid derived from tall oil fatty acids in compliance with § 172.862.

(b) They are used in food in amounts not in excess of that reasonably required to produce their intended effect.

§ 172.858 Propylene glycol alginate.

The food additive propylene glycol alginate (CAS Reg. No. 9005-37-2) may be used as an emulsifier, flavoring adjuvant, formulation aid, stabilizer, surfactant, or thickener in foods in accordance with the following prescribed conditions:

(a) The additive meets the specifications of the Food Chemicals Codex, 3d Ed. (1981), p. 256, which is incorporated by reference (copies are available from the National Academy Press, 2101 Constitution Ave. NW., Washington, DC 20418, or available for inspection at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC 20408), and the additional specification that it shall have up to 85 percent of the carboxylic acid groups esterified with the remaining groups either free or neutralized.

(b) The additive is used or intended for use in the following foods as defined in § 170.3(n) of this chapter, when standards of identity established under section 401 of the act do not preclude such use:

(1) As a stabilizer in frozen dairy desserts, in fruit and water ices, and in confections and frostings at a level not to exceed 0.5 percent by weight of the finished product.

(2) As an emulsifier, flavoring adjuvant, stabilizer, or thickener in baked goods at a level not to exceed 0.5 percent by weight of the finished product.

(3) As an emulsifier, stabilizer, or thickener in cheeses at a level not to exceed 0.9 percent by weight of the finished product.

(4) As an emulsifier, stabilizer, or thickener in fats and oils at a level not to exceed 1.1 percent by weight of the finished product.

(5) As an emulsifier, stabilizer, or thickener in gelatins and puddings at a level not to exceed 0.6 percent by weight of the finished product.

(6) As a stabilizer or thickener in gravies and in sweet sauces at a level not to exceed 0.5 percent by weight of the finished product.

(7) As a stabilizer in jams and jellies at a level not to exceed 0.4 percent by weight of the finished product.

(8) As an emulsifier, stabilizer, or thickener in condiments and relishes at a level not to exceed 0.6 percent by weight of the finished product.

(9) As a flavoring adjunct or adjuvant in seasonings and flavors at a level not to exceed 1.7 percent by weight of the finished product.

(10) As an emulsifier, flavoring adjuvant, formulation aid, stabilizer or thickener, or surface active agent in other foods, where applicable, at a level not to exceed 0.3 percent by weight of the finished product.

(c) To ensure safe use of the additive, the label of the food additive container shall bear, in addition to the other information required by the act:

(1) The name of the additive, "propylene glycol alginate" or "propylene glycol ester of alginic acid".

(2) Adequate directions for use.

[47 FR 29950, July 9, 1982]

§ 172.859 Sucrose fatty acid esters.

Sucrose fatty acid esters identified in this section may be safely used in accordance with the following prescribed conditions:

(a) Sucrose fatty acid esters are the mono-, di-, and tri-esters of sucrose with fatty acids and are derived from sucrose and edible tallow or hydrogenated edible tallow or edible vegetable oils. The only solvents which may be used in the preparation of sucrose fatty acid esters are those generally recognized as safe in food or regulated for such use by an appropriate section in this part. Ethyl acetate or methyl ethyl ketone or dimethyl sulfoxide and isobutyl alcohol (2-methyl-1-propanol) may be used in the preparation of sucrose fatty acid esters.

(b) Sucrose fatty acid esters meet the following specifications:

(1) The total content of mono-, di-, and tri-esters is not less than 80 percent as determined by a method title "Sucrose Fatty Acid Esters, Method of Assay," which is incorporated by reference. Copies are available from the Center for Food Safety and Applied Nutrition (HFS-200), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, or available for inspection at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC 20408.

(2) The free sucrose content is not more than 5 percent as determined by Test S.2 in the method titled "Sucrose Fatty Acid Esters, Method of Assay," which is incorporated by reference. The availability of this incorporation by reference is given in paragraph (b)(1) of this section.

(3) The acid value is not more than 6.

(4) The residue on ignition (sulfated ash) is not more than 2 percent.

(5) The total ethyl acetate content is not more than 350 parts per million as determined by a method titled "Determination of Ethyl Acetate," which is incorporated by reference. Copies are available from the Center for Food Safety and Applied Nutrition (HFS-200), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, or available for inspection at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC 20408.

(6) Arsenic is not more than 3 parts per million.

(7) Total heavy metal content (as Pb) is not more than 50 parts per million.

(8) Lead is not more than 10 parts per million.

(9) The total content of methyl ethyl ketone or of methanol shall not be more than 10 parts per million as determined by a method titled "Methyl Ethyl Ketone Test; Methyl Alcohol Test," which is incorporated by reference. Copies are available from the Center for Food Safety and Applied Nutrition (HFS-200), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, or available for inspection at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC 20408.

(10) The total dimethyl sulfoxide content is not more than 2 parts per million as determined by a method entitled "Determination of Dimethyl Sulfoxide," which is incorporated by reference. Copies are available from the Center for Food Safety and Applied Nutrition (HFS-200), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, or available for inspection at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC 20408.

(11) The total isobuytl alcohol (2-methyl-1-propanol) content is not more than 10 parts per million as determined by a method entitled "Determination of Isobutyl Alcohol," which is incorporated by reference. Copies are available from the Center for Food Safety and Applied Nutrition (HFS-200), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, or available for inspection at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC 20408.

(c) Sucrose fatty acid esters may be used as follows when standards of identity established under section 401 of the Federal Food, Drug, and Cosmetic Act do not preclude such use:

(1) As emulsifiers as defined in § 170.3(o)(8) of this chapter, or as stabilizers as defined in § 170.3(o)(28) of this chapter, in baked goods and baking mixes as defined in § 170.3(n)(1) of this chapter, in chewing gum as defined in § 170.3(n)(6) of this chapter, in coffee and tea beverages with added dairy ingredients and/or dairy product analogues, in confections and frostings as defined in § 170.3(n)(9) of this chapter, in dairy product analogues as defined in § 170.3(n)(10) of this chapter, in frozen dairy desserts and mixes as defined in § 170.3(n)(20) of this chapter, and in whipped milk products.

(2) As texturizers as defined in § 170.3(o)(32) of this chapter in biscuit mixes, in chewing gum as defined in § 170.3(n)(6) of this chapter, in confections and frostings as defined in § 170.3(n)(9) of this chapter, and in surimi-based fabricated seafood products.

(3) As components of protective coatings applied to fresh apples, avocados,

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bananas, banana plantains, limes, melons (honeydew and cantaloupe), papaya, peaches, pears, pineapples, and plums to retard ripening and spoiling.

(d) Sucrose fatty acid esters are used in accordance with current good manufacturing practice and in an amount not to exceed that reasonably required to accomplish the intended effect.

[47 FR 55475, Dec 10, 1982, as amended at 48 FR 38226, Aug 23, 1983; 52 FR 10883, Apr. 6, 1987; 53 FR 22294, 22297, June 15, 1988, 54 FR 24897, June 12, 1989, 60 FR 44756, Aug. 29, 1995]

§ 172.860 Fatty acids.

The food additive fatty acids may be safely used in food and in the manufacture of food components in accordance with the following prescribed conditions:

(a) The food additive consists of one or any mixture of the following straight-chain monobasic carboxylic acids and their associated fatty acids manufactured from fats and oils derived from edible sources: Capric acid, caprylic acid, lauric acid, myristic acid, oleic acid, palmitic acid, and stearic acid.

(b) The food additive meets the following specifications:

(1) Unsaponifiable matter does not exceed 2 percent.

(2) It is free of chick-edema factor:

(i) As evidenced during the bioassay method for determining the chick-edema factor as prescribed in paragraph (c)(2) of this section; or

(ii) As evidenced by the absence of chromatographic peaks with a retention time relative to aldrin (RA) between 10 and 25, using the gas chromatographic-electron capture method prescribed in paragraph (c)(3) of this section. If chromatographic peaks are found with RA values between 10 and 25, the food additive shall meet the requirements of the bioassay method prescribed in paragraph (c)(2) of this section for determining chick-edema factor.

(c) For the purposes of this section:

(1) Unsaponifiable matter shall be determined by the method described in the 13th Ed. (1980) of the "Official Methods of Analysis of the Association of Official Analytical Chemists," which is incorporated by reference. Copies are available from the Association of Official Analytical Chemists International, 481 North Frederick Ave., suite 500, Gaithersburg, MD 20877-2504, or available for inspection at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC 20408.

(2) Chick-edema factor shall be determined by the bioassay method described in "Official Methods of Analysis of the Association of Official Analytical Chemists," 13th Ed. (1980), sections 28.127-28.130, which is incorporated by reference. Copies may be obtained from the Association of Official Analytical Chemists International, 481 North Frederick Ave., suite 500, Gaithersburg, MD 20877-2504, or may be examined at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC 20408.

(3) The gas chromatographic-electron capture method for testing fatty acids for chick-edema shall be the method described in the "Journal of the Association of Official Analytical Chemists," Volume 50 (No. 1), pages 216-218 (1967), or the modified method using a sulfuric acid clean-up procedure, as described in the "Journal of the Association of the Offical Analytical Chemists," Volume 51 (No. 2), pages 489-490 (1968), which are incorporated by reference. See paragraph (c)(2) of this section for availability of these references.

(d) It is used or intended for use as follows:

(1) In foods as a lubricant, binder, and as a defoaming agent in accordance with good manufacturing practice.

(2) As a component in the manufacture of other food-grade additives.

(e) To assure safe use of the additive, the label and labeling of the additive and any premix thereof shall bear, in addition to the other information required by the act, the following:

(1) The common or usual name of the acid or acids contained therein.

(2) The words "food grade," in juxtaposition with and equally as prominent as the name of the acid

[42 FR 14491, Mar. 15, 1977, as amended at 47 FR 11837, Mar 19, 1982 49 FR 10105, Mar. 19 1984, 54 FR 24897, June 12, 1989]

§ 172.861 Cocoa butter substitute from coconut oil, palm kernel oil, or both oils.

The food additive, cocoa butter substitute from coconut oil, palm kernel oil, or both oils, may be safely used in food in accordance with the following conditions:

(a) Cocoa butter substitute from coconut oil, palm kernel oil (CAS Reg. No. 85665-33-4), or both oils is a mixture of triglycerides. It is manufactured by esterification of glycerol with food-grade fatty acids (complying with § 172.860) derived from edible coconut oil, edible palm kernel oil, or both oils.

(b) The ingredient meets the following specifications:

Acid number: Not to exceed 0.5.
Saponification number: 220 to 260.
Iodine number. Not to exceed 3.
Melting range: 30 to 44 °C.

(c) The ingredient is used or intended for use as follows:

(1) As coating material for sugar, table salt, vitamins, citric acid, succinic acid, and spices; and

(2) In compound coatings, cocoa creams, cocoa-based sweets, toffees, caramel masses, and chewing sweets as defined in § 170.3 (n)(9) and (n)(38) of this chapter, except that the ingredient may not be used in a standardized food unless permitted by the standard of identity.

(d) The ingredient is used in accordance with current good manufacturing practice and in an amount not to exceed that reasonably required to accomplish the intended effect.

[56 FR 66970, Dec. 27, 1991; 57 FR 2814, Jan. 23, 1992]

§ 172.862 Oleic acid derived from tall oil fatty acids.

The food additive oleic acid derived from tall oil fatty acids may be safely used in food and as a component in the manufacture of food-grade additives in accordance with the following prescribed conditions:

(a) The additive consists of purified oleic acid separated from refined tall oil fatty acids.

(b) The additive meets the following specifications:

(1) Specifications for oleic acid prescribed in the "Food Chemicals Codex," 3d Ed. (1981), pp. 207-208, which is incorporated by reference, except that titer (solidification point) shall not exceed 13.5 °C and unsaponifiable matter shall not exceed 0.5 percent. Copies of the material incorporated by reference may be obtained from the National Academy Press, 2101 Constitution Ave. NW., Washington, DC 20418, or may be examined at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC 20408.

(2) The resin acid content does not exceed 0.01 as determined by ASTM method D1240-82, "Standard Test Method for Rosin Acids in Fatty Acids," which is incorporated by reference. Copies may be obtained from the American Society for Testing Materials, 1916 Race St., Philadelphia, PA 19103, or may be examined at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC 20408.

(3) The requirements for absence of chick-edema factor as prescribed in § 172.860.

(c) It is used or intended for use as follows:

(1) In foods as a lubricant, binder, and defoaming agent in accordance with good manufacturing practice.

(2) As a component in the manufacture of other food-grade additives.

(d) To assure safe use of the additive, the label and labeling of the additive and any premix thereof shall bear, in addition to the other information required by the Act, the following:

(1) The common or usual name of the acid.

(2) The words "food grade" in juxtaposition with and equally as prominent as the name of the acid.

[42 FR 14491, Mar. 15, 1977, as amended at 49 FR 10105, Mar. 19, 1984]

§ 172.863 Salts of fatty acids.

The food additive salts of fatty acids may be safely used in food and in the manufacture of food components in accordance with the following prescribed conditions:

(a) The additive consists of one or any mixture of two or more of the aluminum, calcium, magnesium, potassium, and sodium salts of the fatty acids conforming with § 172.860 and/or

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Pages 000026 - 000027 have been removed in accordance with copyright laws. Please see appended bibliography list of the references that have been removed from this request.

Appendix 2

Appendix 2: **Article: Chronic Toxicity and Carcinogenicity of Sucrose Fatty Acid Esters in Fischer 344/DUcrj Rats, K. Takeda and M. Flood, *Reg. Tox. Pharm.* 35, 157-164 (2002)**

Pages 000030 - 000037 have been removed in accordance with copyright laws. Please see appended bibliography list of the references that have been removed from this request.

Appendix 3

Appendix 3: Article: Studies on the Metabolic Fate of Sucrose Esters in Rats, Shigeoka *et al.*, *Fd Chem. Toxic.* 22 (1984) 409-414

Pages 000040 - 000045 have been removed in accordance with copyright laws. Please see appended bibliography list of the references that have been removed from this request.

Appendix 4

Appendix 4: Article: Metabolism of ^{14}C-Labelled Sucrose Esters of Stearic Acid in Rats, Noker, Lin *et al.*, *Fd Chem. Toxic.* 35 (1997) 589-595

Pages 000048 - 000054 have been removed in accordance with copyright laws. Please see appended bibliography list of the references that have been removed from this request.

Appendix 5

Appendix 5: FDA Memorandum, November 4, 1993 (ADI for sucrose esters)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date November 4, 1993

From Additives Evaluation Branch No.1 (HFS-226)

Subject Revised ADI for sucrose fatty acid esters (SFAE), conclusions of meeting held Oct 5, 1993, and safety evaluation of pending petitions.

To Novel Ingredients Branch (HFS-207)
Attn: B. Anderson/ M.Cheeseman /D. Keefe
Through Kirk Biddle, Ph.D.
Chief, Additives Evaluation Branch No. 1 (HFS-226)

Food Additive Petition Nos. 0A4183 Mitsubishi Kasei Corp.
2A4321
9A4166 Nebraska Dept. of Economic Development

In the initial evaluation of SFAE in FAP No. 1A 3564, the ADI for SFAE was determined as 450 mg/p/day for a 60 kg individual. This ADI was based on the dog as the most sensitive species using soft stools as the endpoint, and a safety factor of 10 (since the product is hydrolyzed to normal food constituents before absorption) with 0.3 % as the NOEL. We have reexamined the study reports on which the NOEL is based.

In our March 15, 1993 memorandum re: the safety of SFAE we stated: we set the no-effect level (NOEL) for sucrose fatty acid esters (SFAE) in the dog as 1.0% dietary level based on diarrhea as an endpoint.

The study report, on a 26 - week feeding study of mixed sucrose esters of palmitic and stearic acid, a GLP study conducted by Huntingdon Research Centre, and reported in FAP 1A3564 states:

"A dosage-related increase was evident in the incidence of abnormally soft faeces recorded for animals receiving the 1.0% or 3.0% diet. The incidence of this finding in animals receiving 0.3 % diet, however, was comparable to that of control animals." Thus control animals as well as dosed animals exhibited soft feces.

The report continues: " A moderate reduction in the incidence of abnormally soft feces was evident in the control, 0.3 % and 1.0% groups during the second half of the treatment period, while only a slight reduction was recorded in the 3.0 % group over the same period. " The dogs of the low and intermediate dose level groups thus adapted to the high SFAE dietary levels in the course of the study.

These data were confounded by an incident of misdosing over 2 days on week 20 of the study which recorded an increase of the incidence of liquid or soft feces for animals receiving the 1.0 % diet, while coincidentally, a decrease in this clinical sign for animals receiving the 3.0 % diet. As a precaution, the report states, a new batch of diet was formulated for the remainder of the dosing week. Analysis of the diets confirmed that the high-dose group received the 1.0 % diet for these 2 days and the intermediate dose-group received the 3.0 % diet.

We base the NOEL on frank diarrhea because of the evaluation by Dr. Barker in which she states diarrhea is an adverse effect. Diarrhea was a dose-related response of SFAE overtly noted at the 3% dietary level in the dog studies. However, we noted that histopathologically, the large intestine was reported to be normal in both the 6-month study of mixed esters of sucrose palmitate and stearate and the one year study of sucrose palmitate at the 1% dietary level.

We have previously noted that sucrose fatty acid esters are hydrolyzed in the intestine to sucrose and fatty acids, which are normal constituents of the diet. The NOEL of 1 % in the diet translates into 1500 mg/p/day as the ADI for a 60 kg adult using a 10X safety factor based on the hydrolysis of SFAE prior to its absorption. The ADI for the 2-5 yr. age group would be based on a 15 kg individual. This may be calculated as 375 mg/p/d.

CRB (M. DiNovi, personal communication, 5/12/93) states that the EDI estimate includes all products that may be made using SFAE, although competing food emulsifiers may be used for the same purpose. A reasonable consumption figure would be a fraction of the calculated EDI based on all products approved for its incorporation.

Ms. Anderson and Dr. Keefe reported at the meeting of Oct. 5, 1993 (see Memorandum Of Conference, Oct 5, 1993) that none of the petitioners have provided information that reflect on the consumption of SFAE in the U.S. Dr. DiNovi reported that although the 1987 NAS Food Disappearance Survey lists SFAE in the U.S. food supply as zero, he pointed out that the Division of. Product Manufacture and Use (DPMU) bases its EDI on the assumption that the additive will have 100 % market penetration for its intended use. It was agreed at the meeting of Oct. 5, 1993 that

he total reasonable consumption figure would be under the ADI.

The issue of an EDI for the 2 to 5 year age group was also discussed in the in-house conference held Oct 5, 1993 (see memo of Conference op. cit.). It was concluded that because the petitioned uses for SFAE are in surimi, chewing gum, and as emulsifiers in ready-to -drink coffee and tea beverages; and since the 90th percentile intake (EDI) for toddlers are extremely small (surimi 0.1 mg/p/d, and chewing gum 1.9 mg/p/d; DiNovi, memo of 6/3/92) approval of these uses of SFAE will only negligibly increase the level of SFAE in this age group.

The proposed new uses of SFAE are safe because the 90th percentile cumulative consumption level (EDI) for SFAE as estimated by Chemistry Review Branch (CRB, HFS-247) is 718 mg/p/day and the ADI for adults is now considered to be 1500 mg/p/d. The additional intake by the 2 - 5 yr age group will be extremely small (2 mg/p/d) as compared to the ADI for this age group (375 mg/-p/d). On this basis we find the petitions acceptable and ready for regulation.

Marvin J. Bleiberg, Ph.D., DABT

Appendix 6

Appendix 6:

A.	**K&H Summary of JECFA Evaluations**
B.	**Toxicological Monograph from 13th JECFA**
C.	**Toxicological Monograph from 17th JECFA**
D.	**Toxicological Monograph from 20th JECFA**
E.	**Toxicological Monograph from 24th JECFA**
F.	**Toxicological Monograph from 35th JECFA**
G.	**Summary Report from 39th JECFA**
H.	**Toxicological Monograph from 44th JECFA**
I.	**Toxicological Monograph from 49th JECFA**
J.	**JECFA Purity Specifications**

A. K&H Summary of JECFA Evaluations

Summary of JECFA Evaluations of Sucrose Esters of Fatty Acids

We emphasize that JECFA's more recent evaluations of sucrose esters are more relevant and helpful in evaluating their GRAS status today. However, for the sake of presenting a complete picture, we provide the following summary of all of JECFA's evaluations of sucrose esters.

13th JECFA, 1969

JECFA evaluated sucrose esters of fatty acids for the first time at its 13th meeting in 1969. The toxicological monograph prepared after that meeting describes a very large number of studies JECFA considered. Many of the studies do not appear to meet today's standards for animal feeding studies or are not reported in sufficient detail to allow for that determination. Some of the studies appear to be aimed at establishing whether sucrose esters might be useful as a fat substitute, often using feeding levels as high as 25% in the diet. In most cases, very little detail is provided, and JECFA does not explain how much weight, if any, it placed on most of the studies. Many of the studies were published or appear to have been presented in a public forum.

We provide the following summary in chart form of the studies included in JECFA's first evaluation.

Test Substance	Study Description	Conclusions
sucrose monopalmitate	ADME: Berry & Turner (1960) *J. Amer. Oil Chem. Soc.*, 37, 302	JECFA stated that the ester linkage is hydrolyzed with great difficulty by pancreatic or intestinal enzymes *in vitro*. (K&H: This does not appear to rule out hydrolysis by other means, *e.g.*, enzymes not studied by Berry & Turner.)
sucrose monopalmitate	Acute toxicity in mice and rats by intragastric administration	"Intragastric administration of 0.1 g to rats had no effect on the osmotic fragility of erythrocytes but intravenous administration to mice of 0.5 g/kg body weight produced considerable haemolysis."
sucrose monopalmitate	100-day rat study (presumably a feeding study); doses at 0, 1, 2, 3, 5, 10, and 25% of diet.	Deaths noted at 5%, 10%, and 25% doses; at 2% and 3%, only marginal reduction in body weight gain.
sucrose monopalmitate	Two-year dog feeding study at doses up to 3% of diet.	No compound-related differences observed between the test and control groups.
sucrose monopalmitate	Two-year rat feeding study at doses up to 3% of diet.	Data suggested lower body weight gains in the 3% groups; no other differences were noted.

sucrose monopalmitate	3-generation reproduction study in rats over 22 months at 0 or 1% of diet.	Mean litter size, physical appearance and growth of litter were comparable among test and control groups for each generation and among the three filial generations. The autopsies and histological examinations were normal.
sucrose monostearate	ADME: Berry & Turner (1960) *id.*	Some enzymes found not capable of hydrolyzing sucrose monostearate. Only pancreatic juice was able to hydrolyze the ester linkage to a moderate degreee.
sucrose mono-oleate	ADME: Berry & Turner (1960) *id.*	Rat liver homogenates hydrolyzed the ester bond almost completely in 60 minutes; alpha-amylase, lipase, and dog pancreatin equally effective.
sucrose mono-oleate	6-month rat feeding study at doses up to 20% of the diet; Oshima & Kajiwara (1960) *Takeda Kenkyusho Nempo*, 19, 172.	Only at 20% dose, retardation of growth; soft feces or mild diarrhea occurred initially in 10% and 20% dose groups, but animals later became tolerant.
sucrose monolinolenate	ADME study: Sucrose ester or free linolenic acid administered intragastrically to 5 rats with either their thoracic duct cannulated or having a bile and lymph fistula. Tudisco & Turner (1963) *Boll. Soc. Ital. Biol. Sper.*, 39, 1041.	Percentage of linolenic acid absorbed was the same whether sucrose ester or free acid was administered.
Palm Oil Sucrose Esters	ADME: aqueous suspension given intragastrically to rats after pyloric ligation. Balea *et al.* (1966) *Revue Français des Corps Gras*, No. 2, 3	No evidence of digestive hydrolysis up to eight hours.
Palm Oil Sucrose Esters	*In vitro* application of intestinal juice to substrate containing palm oil sucrose esters. Balea *et al.* (1966) *id.*	negligible hydrolysis of ester and glucosidic linkages
Palm Oil Sucrose Esters	Metabolic balance study in rats fed 5% palm oil sucrose esters. Balea *et al.* (1966) *id.*	75% of fed test substance unaccounted for and presumed metabolized.
Palm Oil Sucrose Esters	150-day rat feeding study at 5% and 10%. Tudisco & Chiancone (1965) *Third Congr. Naz. Stud. Alim.*, Bologna	no deleterious effect on body weight gain.
Palm Oil Sucrose Esters mixed with lard	3 rat feeding studies, one lasting 6 months and two lasting 100 days.	weight increases in the test groups noted; other parameters comparable in control and test animals; liver lipids of test animals raised, presumably attributable to lard.
Palm Oil sucrose esters	3 ½ month rat feeding study at 0	No effects noted

	and 2% doses.	
Palm oil sucrose esters	14-month rat feeding study at doses of 0 and 0.5% of diet Chiancone *et al.* (1963) *Ann. Fals. Exp, Chim.*, 56, 193.	Temporary reduction in growth rate in females during weeks 8 to 10; no other effects noted.
Palm oil sucrose esters	25-28 month rat feeding study at doses of 0 or 10% Tudisco & Chiancone (1965) *Third Congr. Naz. Stud. Alim.*, Bologna	No abnormalities noted.
Palm oil sucrose esters	2-generation rat feeding study at doses of 0 and 5 g/kg b.w.	No evidence of any adverse effects on fertility and fetal development was seen.
Lard sucrose esters	ADME study in dogs: Dogs were given intragastrically either (1) ^{131}I-labeled triolein in olive oil; (2) an oil/water emulsion; or (3) an oil/water emulsion containing lard sucrose esters.	Lard sucrose esters did not appear to interfere with intestinal fat absorption.
Lard sucrose esters	ADME study in dogs: Dogs were given intragastrically either (1) $CaCl_2$ in oil/water emulsion; or (2) $CaCl_2$ in oil/water emulsion with lard sucrose esters, using Ca^{45}.	The presence of lard sucrose esters had no consistent effect on Ca absorption.
Lard sucrose esters	ADME study in dogs: Dogs received both I^{131}-labeled triolein and $Ca^{45}Cl_2$ in an oil/water emulsion with and without lard sucrose esters.	Lard sucrose esters had no effect on the pattern of absorption.
Lard sucrose esters	acute study in rats	Rats tolerated doses up to 5 g/kg b.w. lard sucrose ester every 2 hours up to a total of 15 g. Doses of 10 g/kg b.w. every 2 hours up to 30 g produced diarrhea and death from overdistension.
Lard sucrose esters	Single dose in dogs: 3.8 g/kg b.w.	no effect
Lard sucrose esters	Single dose in rabbits: 2 g/kg b.w.	no deleterious effects
Lard sucrose esters	Intragastric administration of 1 g to rats	no osmotic fragility of erythrocytes
Lard sucrose esters	Introgastric administration to rabbits, 3-6 g	no osmotic fragility rise
Lard sucrose esters	intravenous administration to mice, 1-2 g/kg b.w.	no hemolytic effect
Lard sucrose esters	Single oral doses of lard sucrose esters were administered to dogs and compared to doses of refined lard administered to the same dogs after long intervals Tudisco (1963) *Bol. Soc. Ital. Bio. sper.* 39, 1914	No gastro-intestinal disturbances, toxic symptoms, or abnormal findings were noted.
Lard sucrose esters	15-day rat feeding study with	No adverse effects except test

	doses at 0, 5, 10, and 25% of diet Tudisco & Chiancone (1965) *Third Congr. Nax. Stud. Alim.* Bologna	group receiving 25% dose showed reduced body weight gain.
Lard sucrose esters	200-day rat feeding study at doses of 5, 10, and 25% of diet. Controls received lard.	Body weight gain reduced at 10% and especially 25% doses; Food consumption & food efficiency also reduced at 10% and 25% doses; Liver showed frequent "steatosis" at 25% dose; no other effects noted.
Lard sucrose esters	200-day rat feeding study; male rats only received diet containing 25% lard sucrose esters or 18%lard/7%sucrose Tudisco (1967) *Arzneimittel-Forsch.* 17, 350.	No adverse effects on body weight gain, food consumption, or survival. Total liver fat of both test subjects and controls was raised.
Lard sucrose esters	Rats fed 3.6% lard or 5% and 10% lard sucrose esters as only source of lipids for 24-28 months.	No abnormalities found with respect to body weight, general health, mortality, or hematology.
Lard sucrose esters	2-generation rat feeding study at doses of 0 and 5 g/kg b.w. lard sucrose esters.	No adverse effects noted.

After considering these studies, JECFA established a temporary acceptable daily intake (ADI) for sucrose esters of 0-2.5 mg/kg body weight, based upon the two-year rat feeding study of sucrose monopalmitate, in which the no-effect-level was determined to be 1% of the diet. JECFA further emphasized that it seems reasonable to consider mainly the metabolic fate of these compounds and requested (1) further metabolic studies on representative individual sucrose esters; and (2) a two-year feeding study using another sucrose ester in a non-rodent mammalian species.

17th JECFA, 1973

JECFA considered a small amount of additional data in 1973 and produced a very slightly revised toxicological monograph. The new studies in the 1973 monograph include:
(1) acute oral toxicity studies using sucrose monopalmitate in rats and mice (1958);
(2) acute oral toxicity studies using sucrose monostearate in rats and mice (1958);
(3) a 60-day oral toxicity study in rats using sucrose monopalmitate (1959);
(4) a 60-day oral toxicity study in rats using sucrose monostearate (1959); and
(5) 33-day oral toxicity study in rats using mixed palmitic and stearic acid esters of sucrose (1959).

These studies were unpublished but had been submitted to Japan's Ministry of Health and Welfare.

This relatively small amount of additional data did not alter JECFA's evaluation of sucrose esters. The temporary ADI was maintained at 2.5 mg/kg body weight, and

JECFA continued to request (1) further metabolic studies on representative individual sucrose esters; and (2) a two-year feeding study using another sucrose ester in a non-rodent mammalian species.

Beginning with its 1973 evaluation, JECFA has examined the safety of sucrose esters together with sucroglycerides[1] and considers its ADI to be a "group ADI" applicable to both additives.

20th JECFA, 1976

In 1976, JECFA maintained its temporary ADI for sucrose esters at 2.5 mg/kg body weight and refined its request for further information, asking for the following specific information:

1. Studies on individual sucrose esters to demonstrate their likely sites and degree of hydrolysis; and
2. A six-month toxicological study in a non-rodent species on a sucrose ester other than sucrose palmitate.

At this meeting, JECFA reviewed new *in vitro* and *in vivo* metabolism data. Perhaps most significantly, JECFA reviewed a study in which the concentrations of sucrose monopalimtate and palmitic acid were determined in arterial and portal vein blood taken from rats at various time intervals following an oral dose of 500 mg/kg b.w. of purified sucrose monopalmitate. No intact ester could be detected in the blood samples, but the palmitic acid content of arterial blood was raised between 30 and 120 minutes after dosing. This suggests that the ester was hydrolyzed into sucrose and palmitic acid prior to absorption.

JECFA also reviewed a newly submitted 76-week oral toxicity study in mice. The test substance was mixed palmitic and stearic acid esters of sucrose, fed at dietary concentrations of 0, 0.3%, and 3.0%. JECFA's toxicological monograph does not provide a conclusion regarding the no-effect-level in this study. It notes that serum alkaline phosphatase activity was raised in males on the 3% diet, and blood triglyceride levels were elevated in males on the 0.3% and 3.0% diets, but not in females. JECFA considered the significance of these findings uncertain in view of the small number of animals examined.

24th JECFA, 1980

In 1980, JECFA upgraded the ADI for sucrose esters from a temporary ADI of 2.5 mg/kg b.w. to a full ADI of 10 mg/kg b.w. and dropped its request for further studies.

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[1] "Sucroglycerides" are produced by reacting edible fats and oils with sucrose in the presence of a solvent. The product is a mixture of sucrose esters of fatty acids together with mono- and diglycerides.

At this meeting, JECFA examined the studies carried out by Shigeoka *et al.* on the metabolic fate of sucrose esters in rats. These studies were later published in *Food and Chemical Toxicology* (1984, 22, 409-414). A summary of these studies is provided on page 8 of the GRAS Notification. JECFA's toxicological monograph includes the following interpretation of these particular studies:

> In the rat, it is apparent that the sucrose esters are hydrolyzed in the mucosal epithelium cells before intestinal absorption. This observation is also supported by the *in vitro* studies in which rapid hydrolysis of the esters occurs in the presence of mucosal homogenates of the intestine, and only slow hydrolysis in the presence of liver preparations, and negligible hydrolysis by pancreatic juice in the presence of taurocholate.

JECFA also examined published studies on the metabolism of beef tallow sucrose esters in rat and man (Daniel *et al* .(1979) *Food Cosmet. Toxicol.* 17, 19-21). In these studies, rats were given radiolabeled sucrose tallowate in a single oral dose. The disposition of radioactivity in the rats suggested that the esters were hydrolyzed before absorption. Daniel also investigated the metabolic fate of sucrose tallowate in human volunteers. Three volunteers were given one gram of sucrose tallowate, and their 24 hour urines were collected and analyzed for sucrose. Subsequently, the volunteers were given 10 grams of sucrose, and their urine was similarly collected and analyzed. Analysis of the urine following administration of sucrose tallowate indicated the presence of 6, 12, and 13 ppm sucrose in the three volunteers. After administration of 10 grams of sucrose, values of 7, 15, and 24 ppm were obtained. The researchers concluded that the low levels of sucrose in the urine (and presumably the similar levels) provides presumptive evidence that the esters are hydrolyzed to sucrose and the corresponding fatty acids before absorption.

At its 24th meeting, JECFA also considered:
(1) a 26-week oral toxicity study in beagle dogs, in which sucrose tallowate was fed at dietary concentrations up to 3%, showing no adverse, treatment-related effects;
(2) an 18-month oral toxicity study in rats, in which sucrose tallowate was fed at dietary concentrations up to 3%; and
(3) a 26-week oral toxicity study in beagle dogs, in which mixed palmitic and stearic acid esters of sucrose were fed at dietary concentrations up to 3%, showing no adverse, treatment-related effects.

On the basis of these studies, JECFA calculated an ADI of 0-10 mg/kg b.w. More specifically, JECFA based this upon a no-effect-level in rats of 500 mg/kg b.w. A safety factor of only 50 was applied to this NOEL, rather than the standard safety factor of 100, to derive the ADI in humans. JECFA applied the lower safety factor in this case "because these substances are hydrolyzed in the gut to normal food constituents."

35th JECFA, 1984

At its 35th meeting, JECFA considered the consequences of changing the specifications for sucrose esters to include solvent residues of dimethyl sulfoxide (DMSO), isobutanol, and methyl ethyl ketone.

As part of this evaluation, JECFA reviewed several toxicological studies, some of which had been reviewed previously and some of which were newly submitted. These included:

(1) a 26-week feeding study in dogs (mixed palmitic and stearic acid esters);
(2) a 76-week feeding study in mice (mixed palmitic and stearic acid esters);
(3) a 13-week feeding study in rats (palm oil sucroglycerides);
(4) a 132-week feeding study in dogs, along with a shorter range-finding study (palm oil sucroglycerides); and
(5) a 106-108 week feeding study in rats (palm oil sucroglycerides)

On the basis of this review, JECFA concluded that sucrose esters manufactured by a process using DMSO, isobutanol, and/or methyl ethyl ketone could be included in the previously established group ADI of 0-10 mg/kg b.w.

39th JECFA, 1992

At its 39th meeting JECFA sought to clarify the relationship between sucroglycerides and sucrose esters of fatty acids. No new toxicological data were reviewed.

The Committee determined that these materials should be evaluated on the basis of their sucrose ester content. Thus, it was clarified that the group ADI pertains to the sucrose ester content of sucroglycerides and sucrose esters of fatty acids.

JECFA also re-evaluated the long-term rat feeding study of sucrose monopalmitate and determined that the highest dose level, 3% of the diet, represented the NOEL, discounting reduced mean body weights at this dose as being difficult to assess statistically and possibly attributable to poor palatability of the test diet. This evaluation was deemed consistent with a previously reviewed rat feeding study of palm oil sucroglycerides and short-term studies of palm oil sucroglycerides in rats and dogs. Again, because these compounds are hydrolyzed in the gut to give normal dietary constituents, JECFA applied a safety factor of 50 to the NOELs to obtain a new ADI of 0-16 mg/kg b.w.

A full toxicological monograph was not prepared at this meeting, but these results are documented in the published meeting report.

44th JECFA, 1995

At its 44th meeting, JECFA increased the ADI for sucrose esters to 0-20 mg/kg b.w., designated as temporary, and requested a well designed tolerance study in humans to explore the potential for laxation. This evaluation took place at the request of Mitsubishi.

JECFA reviewed absorption, distribution, and excretion studies in rats, dogs, and humans (Hirano *et al.).* [K&H summary: This report covers some work on sucrose mono- and di-esters of fatty acids. Mono-esters are the only sucrose esters found to be slightly absorbed intact. The bioavailability is approximately 0.33% at a dose of 500 mg/kg. At the end of 4 weeks of feeding 5% sucrose mono-stearate (SMS) to rats, the amount of SMS in the liver slowly accumulated to 0.027% of the administered dose. The amount of SMS in the liver was approximately 30 times higher than the amount in any other organ. Little further accumulation occurred in liver after feeding for two years; the amount in the liver after 2 years was only 0.000063% or 0.63 μg/g tissue.]

JECFA also reviewed the 13-week and two-year rat feeding studies sponsored by Mitsubishi. The test substance in these studies was "Ryoto Sugar S-570," in which the fatty acid component is predominantly stearic acid. In each case, the NOEL was deemed to be the highest dose level fed, 5% in the diet or 1970 mg/kg b.w. These rat feeding studies were subsequently published (Takeda and Flood, 2002) and are described in the body of the GRAS Notification on pages 4-6.

At this meeting, JECFA also reviewed information related to possible gastrointestinal effects associated with sucrose esters including observations in humans that were collected as a supplement to the pharmacokinetic study and special studies on gastrointestinal effects in mice and dogs.

JECFA was concerned about the possibility of laxation in humans, but noted several deficiencies in the human tolerance study, such as the small number of test subjects and the absence of a control group. Accordingly, JECFA requested a follow-up well designed and conducted human tolerance study. JECFA's concerns regarding the possibility of laxation at high doses was not so great, however, that it prevented the establishment of an increased ADI, albeit temporary, at 20 mg/kg b.w.

49th JECFA, 1998

At this meeting, JECFA increased the ADI for sucrose esters to the current 30 mg/kg b.w. and designated this as a full, rather than temporary, ADI.

JECFA reviewed a well conducted human tolerance study submitted by Mitsubishi and agreed that it showed no effects at the highest doses, equal to 27 and 29 mg/kg b.w. in men and women respectively.

JECFA noted that the two-year rat feeding study submitted previously by Mitsubishi would support an ADI of 0-40 mg/kg b.w. if the reduced safety factor of 50 were once again applied to the NOEL. However, JECFA deemed it appropriate to cap the ADI at 30 mg/kg b.w., corresponding to the high dose and no-effect-level in the newer human tolerance study, as the possibility of laxation at higher doses could not be excluded.

JECFA's Purity Specifications for Sucrose Esters of Fatty Acids

JECFA most recently established purity specifications for sucrose esters of fatty acids at its 53rd meeting in 1999). JECFA's specifications are similar to those established by FDA and those appearing in the Food Chemicals Codex. They specify that sucrose esters consist primarily (≥ 80%) of mono-, di-, and tri-esters of sucrose with food fatty acids.

B. Toxicological Monograph from 13th JECFA

Pages 000073 - 000083 have been removed in accordance with copyright laws. Please see appended bibliography list of the references that have been removed from this request.

C. Toxicological Monograph from 17th JECFA

Pages 000086 - 000095 have been removed in accordance with copyright laws. Please see appended bibliography list of the references that have been removed from this request.

D. Toxicological Monograph from 20th JECFA

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E. Toxicological Monograph from 24th JECFA

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F. Toxicological Monograph from 35th JECFA

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G. Summary Report from 39th JECFA

Pages 000120 - 000123 have been removed in accordance with copyright laws. Please see appended bibliography list of the references that have been removed from this request.

H. Toxicological Monograph from 44th JECFA

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I. Toxicological Monograph from 49th JECFA

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J. JECFA Purity Specifications

Pages 000138 - 000148 have been removed in accordance with copyright laws. Please see appended bibliography list of the references that have been removed from this request.

SUBMISSION END

000149

Reference List for Industry Submission, GRN 000129

Pages	*Author*	*Title*	*Publish Date*	*Publisher*	*BIB_Info*
000026 - 000027	NA	Sucrose Fatty Acid Esters	1997	Food Chemicals Codex / Monograph Specifications	First Supplement to the Fourth Edition, pgs 44-45
000030 - 000037	Takeda, K.; Flood, M.	Chronic Toxicity and Carcinogenicity of Sucrose Fatty Acid Esters in Fischer 344/DuCrj Rats	2002	Regulatory Toxicology and Pharmacology	Volume 35, pgs 157-164
000040 - 000045	Shigeoka, T.; Izawa, O.; Kitazawa, K.; Yamauchi, K.; Murata, T.	Studies On The Metabolic Fate of Sucrose Esters In Rats	1984	Food and Chemical Toxicology	Volume 22, Number 6, pgs 409-414
000048 - 000054	Noker, P.E.; Lin, T.-H.; Hill, D.L.; Shigeoka, T.	Metabolism of 14C-Labelled Sucrose Esters of Stearic Acid in Rats	1997	Food and Chemical Toxicology	Volume 35, pgs 589-595
000073 - 000083	NA	Toxicological Evaluation of Some Food Colours, Emulsifiers, Stabilizers, Anti-Caking Agents and Certain Other Substances: Sucrose Esters of Fatty Acids	1969	FAO Nutrition Meeting Report Series	Number 46A WHO/FOOD ADD/ 70.36
000086 - 000095	World Health Organization	Toxicological Evaluation of Some Food Additives Including Anticaking Agents, Antimicrobials, Antioxidants, Emulsifiers and Thickening Agents: Sucrose Esters of Fatty Acids, and Sucroglycerides	1974	WHO FOOD Additives	Series Number. 5
000097 - 000107	Joint FAO/WHO Expert Committee on Food Additives	Toxicological Evaluation of Certain Food Additives: Sucrose Esters of Fatty Acids, and Sucroglycerides	1976	WHO FOOD Additives Series	Series Number 10
000109 - 000113	Joint FAO/WHO Expert Committee on Food Additives	Sucrose Esters of Fatty Acids and Monoglycerides	1979	WHO FOOD Additives Series	NA
000115 - 000118	Joint FAO/WHO Expert Committee	Sucrose Esters of Fatty Acids and Sucroglyceride	NA	WHO	NA

NA- Not applicable

Pages	Author	Title	Publish Date	Publisher	BIB_Info
000120 - 000123	Joint FAO/WHO Expert Committee on Food Additives	Evaluation of Certain Food Additives and Naturally Occurring Toxicants: Sucrose Esters of Fatty Acids and Sucroglycerides	1992	WHO Technical Report Series	Thirty-Ninth Report, Number 828, pages 6-8
000125 - 000132	Vavasour, Elizabeth	Sucrose Esters of Fatty Acids and Sucroglycerides	NA	INCHEM	NA
000134 - 000136	Joint FAO/WHO Expert Committee on Food Additives	Safety Evaluation of Certain Food Additives and Contaminants: Sucrose Esters of Fatty Acids and Sucroglycerides	1998	World Health Organization	Series Number 40
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NA- Not applicable