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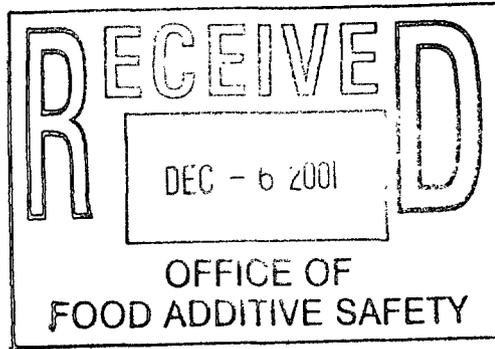
ORIGINAL SUBMISSION

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December 5, 2001

**Hand Delivered**

Dr. Alan Rulis  
Office of Food Additive Safety (HFS-200)  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
200 C Street, S.W.  
Washington, D.C. 20204



WRITER'S DIRECT ACCESS

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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 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.

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 yours,

David R. Joy

Enclosure

cc: Mr. Y. Umeki

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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 carotene color preparations.

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

December 5, 2001

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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. The maximum level of use is expected to be 2% sucrose esters in the color preparation.

Colored beverages often contain lipophilic carotenoids as colorants. To color an aqueous beverage 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 beverage itself is 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 4 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.

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 4<sup>th</sup> 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. Information Relevant to Self-limiting Levels of Use

Not applicable.

4. 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 a 13-week and a 2-year feeding study conducted in Fischer 344/DuCrj rats. We also note that the safety of sucrose fatty acid esters for various food applications has been evaluated favorably in the past by the Food and Drug Administration and the Joint (FAO/WHO) Expert Committee on Food Additives (JECFA).

i. Chronic Toxicity and Carcinogenicity Study

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, 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 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 50 male and 50 female rats in the carcinogenicity study. Animals in satellite groups of 14 rats/sex/group were sacrificed at 12 months to evaluate chronic toxicity. There were no S-570-related effects on survival, tumor incidence or time-to-tumor, ophthalmology, hematology, clinical chemistry, organ weights, or histopathology. These results indicate that S-570 is not toxic or carcinogenic when fed to rats at up to 5% of the diet for 2 years.

A report of this study is provided in the article presented as Appendix 2.

FDA has evaluated the above-described safety study in the course of reviewing pending Food Additive Petition No. 8A4610. JECFA has evaluated the same study and concluded that "No adverse effects of treatment were demonstrated in the long-term

toxicity/carcinogenicity study conducted in rats at dose levels up to 50 g/kg in the diet, equal to 1970 mg/kg bw/day.” (Appendix 9 - 44<sup>th</sup> JECFA).

ii. Other Safety Information

Sucrose esters have been permitted and used in foods as emulsifiers for many years in Japan, Europe, and North America. 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. A84610). 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 two-year rat feeding study 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. This and other information is summarized below.

a. FDA’s Acceptable Daily Intake

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 sucrose esters. The agency’s conclusions are embodied in a memorandum dated November 4, 1993, which is presented as Appendix 3. FDA assigned an ADI of 25 mg/kg b.w. to sucrose esters, expressed as 1500 mg/p/day for a 60-kg adult.

b. JECFA’s Acceptable Daily Intake

Sucrose esters and/or sucroglycerides were evaluated by JECFA at its 13<sup>th</sup>, 17<sup>th</sup>, 20<sup>th</sup>, 24<sup>th</sup>, 35<sup>th</sup>, 44<sup>th</sup>, and 49<sup>th</sup> meetings. The most recent evaluation resulted in “a group ADI of 30 mg/kg bw for the sucrose ester content of sucrose esters of fatty acids and sucroglycerides.” The toxicological monographs prepared by JECFA are presented as Appendices to this Notification as follows.

13 <sup>th</sup> JECFA, 1969:	Appendix 4
17 <sup>th</sup> JECFA, 1973:	Appendix 5
20 <sup>th</sup> JECFA, 1976:	Appendix 6
24 <sup>th</sup> JECFA, 1980:	Appendix 7
35 <sup>th</sup> JECFA, 1989:	Appendix 8
44 <sup>th</sup> JECFA, 1995:	Appendix 9
49 <sup>th</sup> JECFA, 1997:	Appendix 10

The Notifier recognizes FDA's view that a favorable JECFA evaluation is not, by itself, adequate support for a GRAS determination. The JECFA evaluations are included in the submission because they provide a helpful summary of the extant safety data for sucrose esters and because they help to fulfill the expert consensus element of GRAS status.

JECFA's ADI of 30 mg/kg bw is derived from the two-year feeding study in rats summarized above and more fully described in the enclosed article (Appendix 2). JECFA noted that the NOEL of 2000 mg/kg bw per day combined with a safety factor of 50 would allow for an ADI of 0-40 mg/kg bw. The lower safety factor of 50 was considered appropriate for sucrose esters of fatty acids because these compounds are hydrolyzed to normal dietary constituents, sucrose and fatty acids, in the gastrointestinal tract prior to absorption. JECFA limited the ADI to 30 mg/kg bw, however, because the potential for sucrose esters to induce laxative effects at doses exceeding 30 mg/kg bw per day could not be ruled out on the basis of available human tolerance studies.

The human tolerance studies are summarized in the toxicological monograph prepared by the 49<sup>th</sup> JECFA (Appendix 10).

Absorption, distribution, and excretion studies in rats, dogs, and humans were considered by JECFA and are summarized in the toxicological monograph prepared by the 44<sup>th</sup> JECFA (Appendix 9). These studies demonstrate that very small amounts of the monoester are absorbed as such in all three species. It is unlikely that the diester is absorbed as such. Diesters and higher esters are either hydrolyzed to free sucrose and fatty acids prior to absorption, or they pass unchanged through the gastrointestinal tract. The small amounts of absorbed monoesters are metabolized to sucrose and fatty acids and either excreted as carbon dioxide or integrated into body components.

A reproduction study in rats was considered by JECFA and is summarized in the toxicological monograph prepared by the 20<sup>th</sup> JECFA (Appendix 6). The study was carried out on groups of eight male and 16 female rats over 22 months using sucrose monopalmitate at 0 or 1% of the diet. The parent generation was mated twice to give F<sub>1A</sub> and F<sub>1B</sub> filial generations. Sixteen F<sub>1B</sub> females and eight F<sub>1B</sub> males were mated twice to produce F<sub>2A</sub> and F<sub>2B</sub> generations. Sixteen females and eight males from the F<sub>2B</sub> generation were mated twice to produce the F<sub>3A</sub> and F<sub>3B</sub> generation. 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. Autopsies and histopathological examinations were considered normal.

### iii. Safety Determination

As estimated below, the intake of sucrose esters associated with their use in beta-carotene color preparations is on the order of 0.5 mg/person/day, or roughly 10 µg/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, 10 µg/kg b.w. is 2500 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.

We also note that in 1995 FDA estimated total dietary exposure to sucrose esters associated with all uses currently authorized under section 172.859 (May 23, 1995 memorandum to L. Tarantino; copy presented as Appendix 11). FDA's 90<sup>th</sup> percentile figure is 1 mg/kg body weight for a 60-kg adult. This leaves a substantial amount of room between the cumulative exposure to sucrose esters associated with currently cleared uses, together with the use that is the subject of this Notification, and the ADI, 25 mg/kg b.w. or 30 mg/kg b.w. according to JECFA.

iv. Intake Estimate

The intake of sucrose esters associated with their use in beta-carotene 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 2% in beta-carotene color preparations intended for use in orange-colored beverages such as soft drinks and juice beverages. Typically, about 3 to 6 ppm of pure beta-carotene is needed to color a beverage. Beta-carotene color preparations contain beta-carotene blended with other ingredients. An example is Roche's Beta-Carotene 5% Emulsion product, which will contain 0.5% to 2% sucrose esters and 5% beta-carotene. If this product is used to introduce 6 ppm beta-carotene into a beverage, the Beta-Carotene 5% Emulsion must be added to the beverage at a level of 120 ppm. A 240 ml serving of that beverage would then contain 0.576 mg of sucrose esters, assuming the beverage has a specific gravity of 1 g/ml. (240 g x 120 ppm x 2% sucrose esters). For a 60-kg adult, this level of intake for sucrose esters may be expressed as 9.6 µg/kg body weight.

v. 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 a two-year rat feeding study has been accepted for publication in a peer-reviewed scientific journal. Included with Appendix 2 is a letter from editors of *Regulatory Toxicology and Pharmacology* indicating that the article has been accepted for publication. The publisher, Academic Press, has informed us that the article is scheduled to appear in the February, 2002 edition of the journal.

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 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.

We have searched the published scientific literature for other reports that might support or detract from a conclusion that sucrose esters of fatty acids are GRAS under the conditions of use described in this Notification. Several studies were published relating to the safety of olestra, the octa-ester of sucrose with fatty acids. The safety of olestra is based largely upon its non-absorption. In addition to the article presented as Appendix 2, at least one other article deals directly with the safety of the lower esters: "The Metabolism of Beef Tallow Sucrose Esters in Rat and Man," Daniel and Marshall, *Fd. Cosmet. Toxicol.* Vol 17, pp 19-21 (1979). This article concludes that because of the ease with which the lower sucrose esters are hydrolyzed to sucrose and the corresponding fatty acids, their use as food additives does not appear to present a significant toxicological hazard.

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 two-year S-570 feeding study 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.



**APPENDIX 1**

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

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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 adjunct, 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 29850, July 9, 1992]

**\$ 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 hydro-generated edible tallow or hydro-soluble 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 titled "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, 200 C St. SW., Washington, DC 20204, 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, 200 C St. SW., Washington, DC 20204, 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, 200 C St. SW., Washington, DC 20204, or available for inspection at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC 20408.

(10) 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 hydro-generated edible tallow or hydro-soluble 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 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, 200 C St. SW., Washington, DC 20204, or available for inspection at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC 20408.

(1) The total isobutyl 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, 200 C St. SW., Washington, DC 20204, 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(m)(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, bananas, banana plantains, limes, melons (honeydew and cantaloupe), pa-

**Food and Drug Administration, HHS**

pears, 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 44766, Aug. 28, 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.

(1) 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,

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Pages 000014 - 000015 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**

**Article: Chronic Toxicity and Carcinogenicity of  
Sucrose Fatty Acid Esters in Fischer 344/DUcrj Rats,  
K. Takeda and M. Flood**

**000017**

# REGULATORY TOXICOLOGY AND PHARMACOLOGY

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July 9, 2001

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RE: *“Chronic Toxicity and Carcinogenicity of Sucrose  
Fatty Acid Esters in Fischer 344/DUcrj Rats”*  
TAKEDA, K. and M. Flood - MS. #F-1085

Dear Mr. Joy:

We are pleased to receive the revised manuscript cited above and are proceeding with publication plans in RTP.

Please have the enclosed copyright agreement signed and returned to Academic Press. The galley proofs will be sent to Dr. Flood via .pdf file and I have taken the liberty of using his address as Flood@khlaw.com. If this is incorrect, please advise his correct address.

Thank you and best regards.

Sincerely,

Sallie Carr

/sc

Enclosures

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July 2, 2001

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Via Federal Express

Dr. C. Jelleff Carr  
Managing Editor  
Regulatory Toxicology and Pharmacology  
6546 Belleview Drive  
Columbia, Maryland 21046

Re: 90-Day and Two-Year Feeding Studies; Sucrose Fatty Acid Esters;  
TAKEDA and Flood, MS. #F-1085

Dear Dr. Carr:

Enclosed, in duplicate, is the final version of a manuscript that one of our staff scientists, Michael Flood, has prepared for publication in *Regulatory Toxicology and Pharmacology*. We submitted the original draft manuscript several months ago and received comments from a peer reviewer in February, 2001. We have explored the issues raised by the peer reviewer with the laboratory that performed the study and, where appropriate, have made minor revisions to the article. The comments of the peer reviewer are also enclosed for your convenient reference.

000019

Dr. C. Jelleff Carr  
July 2, 2001  
page 2

With these changes, we would like to have the enclosed version of the article published. Please let us know if you have any questions or comments or if any additional information is needed from us.

Cordially yours,

David R. Joy

Enclosure

cc: Mr. Youichiro Umeki

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**APPENDIX 3**

**FDA Memorandum, November 4, 1993**

**000043**

  
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.

000044

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

the 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

000046



**APPENDIX 4**

**Toxicological Monograph from 13<sup>th</sup> JECFA**

**000048**

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**APPENDIX 5**

**Toxicological Monograph from 17<sup>th</sup> JECFA**

**000062**

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**APPENDIX 6**

**Toxicological Monograph from 20<sup>th</sup> JECFA**

**000074**

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**APPENDIX 7**

**Toxicological Monograph from 24<sup>th</sup> JECFA**

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**APPENDIX 8**

**Toxicological Monograph from 35<sup>th</sup> JECFA**

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**APPENDIX 9**

**Toxicological Monograph from 44<sup>th</sup> JECFA**

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**APPENDIX 10**

**Toxicological Monograph from 49<sup>th</sup> JECFA**

**000110**

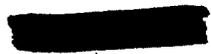
Pages 000111 - 000113 have been removed in accordance with copyright laws. Please see appended bibliography list of the references that have been removed from this request.

**APPENDIX 11**

**FDA Memorandum, May 23, 1995**

**000114**

000115





## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

## Memorandum

Date May 23, 1995

From Chemistry Review Branch, HFS-247

Subject FAP's 9A4166, 2A4321, and 0A4183. Sucrose Fatty Acid Esters (SFAE). Evaluation of Probable Exposure.

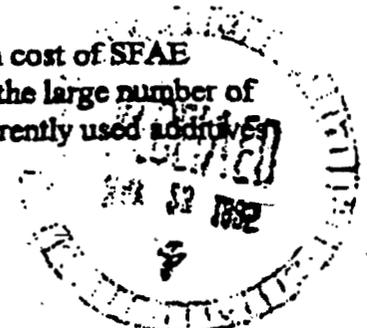
To Division of Product Policy, HFS-206  
L. Tarantino, Ph.D.

We have been asked to refine our estimate of the probable exposure to sucrose fatty acid esters (21 CFR 172.859), based on data submitted at a meeting on May 18, 1995 by Keller and Heckman (agents for the Mitsubishi Kasei Corporation, one of the petitioners for SFAE use expansion) concerning the use of emulsifiers in food. We have previously estimated exposure to SFAE, for the combined current and proposed uses, using a Monte Carlo analysis of food intakes and SFAE use levels (mean, all ages: 412 mg/p/d, 90th percentile, 718 mg/p/d; mean, 2-5 years: 315 mg/p/d; 90th percentile, 545 mg/p/d). These estimates are contained in the memorandum of 6-2-92.

These estimates were made using the assumption that SFAE will replace all of the emulsifiers in a consumer's diet. This assumption was needed for lack of information pertaining to more specific usage of SFAE, although it is highly exaggerative for a number of reasons. First, emulsifiers are ubiquitous in prepared foods and are "invisible" to the consumer, that is, their presence or absence would not affect a consumer's choice of a food containing a given emulsifier as opposed to a different emulsifier. Second, according to the most recent National Academy of Sciences (NAS) survey of food additive usage (1987) no fewer than 43 emulsifiers are available to food processors. This makes the total replacement of all emulsifiers in all food categories by a single emulsifier in a given consumers diet extremely improbable, given the specific nature and technical limits on the use of some emulsifiers in food.

The petitioner has submitted a table (see attached) containing the 1987 poundages of all emulsifiers used in foods as surveyed by the NAS. Total poundage was 71 million pounds. 000116  
Because emulsifiers are ubiquitous in processed foods, it is reasonable to assume that all consumers are eaters of one emulsifier or another. Also, because the market for emulsifiers is fully mature, there is no reason to expect an expansion of uses that could cause an appreciable increase in exposure in the future. Therefore, a per-capita estimate of mean intake, based on the submitted data, is appropriate. For the population of 243 million in 1987, per-capita emulsifier exposure was 362 mg/p/d.

The petitioner has stated at a meeting on May 18, 1995 at FDA that the high cost of SFAE restricts its use to those foods where its functionality is high. Additionally, the large number of available substitutes suggests that SFAE could only replace a portion of currently used additives.



(it should be noted that in the 1987 poundage survey, no use of SFAE was reported). If SFAE were to replace, for example, 10% of the current poundage, i.e., 7.1 million pounds, it would become the third highest use emulsifier behind mono- and diglycerides (42 million pounds) and lecithin (13.1 million pounds). We suggest that, for the reasons cited above, this is unlikely. However, if this were the case, exposure to SFAE would be 36 mg/p/d (mean) and 63 mg/p/d (90th percentile, assuming the same ratio of 90th percentile to mean as found in the 6-2-92 exposure memorandum noted above). The 90th percentile figure is 1 mg/kg-bw for a 60 kg adult or 4 mg/kg-bw for a 2-5 year old (15 kg), conservatively assuming that the exposure remained at 63 mg/p/d for a 2-5 year old<sup>1</sup>.

**Based on this information, we estimate that probable exposure to SFAE for all current and anticipated uses at the 90th percentile intake level is no more than 63 mg/p/d.**

Michael DiNovi, Ph.D.

000117

<sup>1</sup>Our previous exposure estimate for 2-5 year olds was approximately 75% that of adults.

Name In Survey	NAS Code Number	CFR Citation	1987
mono-and diglycerides	0130	184.1505	41,800,000
Lecithin	0104	184.1400	13,100,000
sodium stearoyl lactylate	1170	172.846	5,660,000
glyceryl monostearate	2527	182.1324	2,210,000
ethoxylated mono- and diglycerides	1070	172.834	1,380,000
polysorbate 60	2916	172.836 et al.	1,320,000
polysorbate 80	2917	172.840 et al.	1,160,000
propylene glycol stearate	2942	172.856	1,100,000
glyceryl-lacto esters of fatty acids	1088	172.852	662,000
diacetyl tartaric acid esters of mono- and diglycerides (DATEM)	0076	184.1101	652,000
propylene glycol mono-and diesters of fatty acids	1153	172.856 et al.	524,000
acetylated mono-glycerides	0530	172.828	451,000
calcium stearoyl lactylate	0538	172.844	330,000
sorbitan monostearate	3028	172.84 et al.	200,000
calcium stearate	0260	184.1229	132,000
hydroxylated lecithin	1094	172.814	75,700
glycerol monooleate	2526	172.515	50,600
sodium stearyl fumarate	1156	172.826	10,300
polysorbate 20	2915	172.515	7,850
oxystearin	1125	172.818 et al.	4,280
polysorbate 65	9535	172.838 et al.	3,730
succinylated monoglycerides	1176	172.830	3,240
monoglyceride citrate	0131	172.832	1,040
sodium lauryl sulfate	0347	172.822	1,000
monosodium phosphate derived mono- and diglycerides	0135	184.1521	830

000118

Name in Survey	Code Number	CFR Citation	1987
sorbitan monooleate	8770	173.75	460
dioctyl sodium sulfosuccinate	1066	172.810	71
polyoxyethylene (600) dioleate	1140	173.340	NRP
sodium dodecyl-benzene sulfonate	1243	173.315	NRP
stearyl monoglyceride citrate	1175	172.755	NRP
succistearin	1177	172.765	NRP
sucrose fatty acid esters	1409	172.859	NRP*
lactylic esters of fatty acids	1102	172.848	*
lactylic fatty acid esters of glycerol and propylene glycol	1101	172.850	NRP
methyl glucoside-coconut oil ester	1114	172.816	NRP
glycerol lactopalmitate	0281	172.852	*
polyoxyethylene (600) monoricinoleate	1141	173.340	NRP
sodium mono- and dimethyl naphthalene sulfonates	1165	172.824	NRP
sodium lignosulfonate	1247	173.310	NRP
sodium methyl sulfonate	1404	173.385	NRP
sodium n-alkyl-benzene sulfonate	1241	173.315	NRP
sodium 2-ethyl-hexyl sulfate	1244	173.315	NRP
sodium decyl benzene sulfonate	1161	172.210	NRP
Total emulsifier pounds			70,998,000

NRP = no reported poundage; no firm reported using

\* = no reported poundage, but there were reports of usage from one to three firms.

$$\text{Per capita intake} = \frac{71.0 \text{ million lbs.}}{243 \text{ million people}} \times \frac{454 \text{ g/lb.}}{365 \text{ d/yr.}}$$

$$= 362 \text{ mg/d}$$

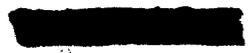
$$\text{Per capita, in mg/kg bw} = 362 \text{ mg/d} \div 60 \text{ kg bw} = 6.0 \text{ mg/kg}$$

$$\text{Per capita, as \% of sucrose ester ADI} = \frac{6.0}{20} \times 100\% = 30\%$$

000119

000120

SUBMISSION END



## *Reference List for Industry Submission, GRN 000092*

<i>Pages</i>	<i>Author</i>	<i>Title</i>	<i>Publish Date</i>	<i>Publisher</i>	<i>BIB_Info</i>
000014 - 000015	NA	Monograph Specifications: Sucrose Fatty Acid Esters	NA	Food Chemicals Codex	Fourth Edition, First Supplement, pgs 44-45
000021 - 000041	Takeda, K.; Flood, M.	Chronic Toxicity and Carcinogenicity of Sucrose Fatty Acid Esters In Fischer 344/DUcrj Rats	NA	NA	pgs 1 - 16
000049 - 000060	Joint FAO/WHO Expert Committee on Food Additives	Toxicological Evaluation of Some Food Colours, Emulsifiers, Stabilizers, Anti-Caking Agents and Certain Other Substances: Sucrose Monopalmitate	1969	FAO Nutrition Meetings Report Series	Number 46A WHO/FOOD ADD/70.36
000063 - 000072	Joint FAO/WHO Expert Committee on Food Additives	Toxicological evaluation of some food additives including anticaking agents, antimicrobials, antioxidants, emulsifiers and thickening agents: Sucrose Monopalmitate	1974	WHO Food Additives Series	Number 5
000075 - 000085	Joint FAO/WHO Expert Committee on Food Additives	Toxicological Evaluation of Certain Food Additives: Sucrose Monopalmitate	1976	WHO Food Additives Series	Number 10
000088 - 000092	Joint FAO/WHO Expert Committee on Food Additives	Sucrose Esters of Fatty Acids and Monoglycerides: Sucrose Monostearate	NA	NA	NA
000095 - 000098	Joint FAO/WHO Expert Committee on Food Additives	Sucrose Esters of Fatty Acids and Sucroglyceride: Mixed Palmitic and Stearic Acid Esters of Sucrose	NA	NA	NA
000101 - 000108	Vavasour, Elizabeth	Sucrose Esters of Fatty Acids and Sucroglycerides	NA	NA	NA
000111 - 000113	Joint FAO/WHO Expert Committee on Food Additives	Safety Evaluation of Certain Food Additives and Contaminants: Sucrose Esters of Fatty Acids and Sucroglycerides	1998	WHO Food Additives Series	Number 40

*NA- Not applicable*

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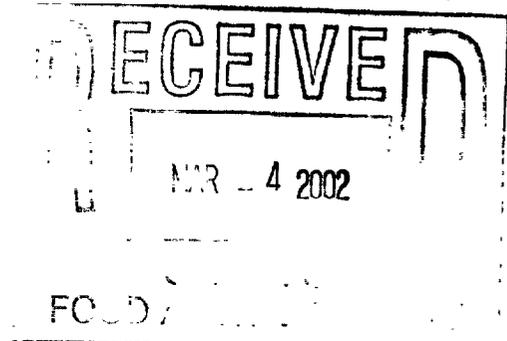
WRITER'S DIRECT ACCESS

March 1, 2002

**John S. Eldred**  
(202) 434-4176  
Eldred@khlaw.com

**Via Facsimile and Federal Express**

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



Re: GRAS Notice No. GRN 000092

Dear Dr. Rulis:

We are writing to express our respectful disagreement with the conclusion reached in your letter of February 4, 2002, regarding the above-referenced GRAS Notification, which we submitted December 5, 2001, on behalf of Mitsubishi Chemical Corporation, and to request your reconsideration of this matter.

The letter states that GRN 92 does not provide a sufficient basis for a determination that sucrose fatty acid esters (hereinafter "sucrose esters") are generally recognized as safe ("GRAS") under the described conditions of use. We believe this conclusion is based upon a both a misreading of the Notification and a misapplication of the legal criteria for GRAS status. We recognize that FDA is not questioning the safety of sucrose esters in the described application. The only question is whether the information presented in GRN 92 provides a sufficient basis for a GRAS determination.

The Notification claims GRAS status for the use of sucrose esters as an emulsifier in  $\beta$ -carotene color preparations. The Notification presents a dietary intake estimate associated with this use of approximately 0.5 mg/person/day, with which the Agency seems to agree. The Notification relies primarily upon a two-year rat feeding study which has been accepted for publication in a peer reviewed scientific journal, *Regulatory Toxicology and Pharmacology*. The Notification also relies upon numerous favorable published evaluations of sucrose esters undertaken by the Joint (FAO/WHO) Expert Committee on Food Additives (JECFA), which provide detailed information on, e.g., the two-year feeding study. The Notification cites FDA's own well-documented acceptable daily intake (ADI) of 25 mg/kg body weight for sucrose esters,

**000139**

as well as FDA's estimation that all currently cleared uses for sucrose esters contribute to an estimated daily intake of approximately 1 mg/kg body weight. FDA explained its derivation of the ADI and its intake estimate for sucrose esters in two published and publicly available memoranda.<sup>1</sup> The narrow food application covered by GRN 92 would result in an estimated daily intake of roughly 0.5 mg/person/day, or 0.01 mg/kg body weight.<sup>2</sup>

Sucrose esters have been safely used in food applications for almost 20 years in the United States.<sup>3</sup> The application covered by GRN 92 represents a minuscule increase in dietary exposure to sucrose esters, an additional 0.01 mg/kg body weight, which is 2500 times lower than FDA's own published ADI for sucrose esters. GRN 92 relies upon a two-year rat feeding study accepted for publication in a peer-reviewed scientific journal. This and the extensive published review of this study by JECFA satisfies the requirement that the pivotal safety data be publicly and generally available. An overwhelming abundance of other corroborating data and published expert opinion exists including human clinical studies. Given these abundantly clear indications of safety and general recognition thereof, we are puzzled and disturbed by the Agency's swift rejection of GRN 92.

The Agency's February 4, 2002, response letter identifies three bases for the decision: (1) that the two-year rat feeding study is only scheduled for publication but does not currently appear in print; (2) that even publication of the two-year rat feeding study may be inadequate to confer GRAS status because there must be a time gap between publication and achievement of GRAS status; and (3) that most of the safety studies reviewed by JECFA are not generally available to the public. We deal with each of these issues below.

#### *Public Availability of the Two-Year Rat Feeding Study*

The Agency's February 4, 2002, letter does not indicate how much weight the Agency placed on the article's pre-publication status. The letter refers to the article as an "unpublished" manuscript, but does not otherwise comment on this point. In case the pre-publication status of the article was considered a significant weakness in the submission, we address this issue.

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<sup>1</sup> The two memoranda were cited as references in the August 29, 1995, Federal Register in the context of a final rule expanding the permitted uses of sucrose esters (60 Fed. Reg. 44756). The memoranda were placed on public display in the Dockets Management Branch. (GRN 92, Appendices 3 and 11)

<sup>2</sup> GRN 92, page 7.

<sup>3</sup> The food additive clearance for sucrose esters, 21 C.F.R. § 172.859, was promulgated on December 10, 1982 (47 Fed. Reg. 55475).

GRN 92 includes as Appendix 2 a letter dated July 9, 2001, from the Associate Managing Editor of *Regulatory Toxicology and Pharmacology* stating that the two-year study has been accepted for publication. GRN 92 also states our understanding that the article describing the study would appear in the February issue of the journal. The journal has since informed us that the article is scheduled to appear in the April issue.

While we recognize the Agency has, in general,<sup>4</sup> required publication of safety data as a prerequisite to a GRAS submission, in this case to insist that publication actually occur prior to submission of the GRAS Notification exalts form over substance and serves no useful purpose in protection of the public health. In this case, the existence of the study, and extensive details about its results, not to mention acceptance of the study by the world's leading authorities in food ingredient safety evaluation, are contained in the JECFA toxicological monograph<sup>5</sup> which has been published and in the public domain for over five years. Quite arguably and reasonably, it is not even necessary for the study itself to be published at all in order for sucrose esters to achieve GRAS status for use in  $\beta$ -carotene color preparations. This is because the study is described in adequate detail in JECFA's toxicological monograph.<sup>6</sup> But our client

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<sup>4</sup> The GRAS criteria as currently defined in the Code of Federal Regulations state that "general recognition of safety through scientific procedures shall *ordinarily* be based upon published studies . . ." (emphasis added). 21 C.F.R. § 170.30(b). The GRAS Notification proposal repeats and elaborates upon this idea, stating that "the *usual* mechanism to establish that scientific information is generally available is to show that the information is published in a peer-reviewed scientific journal" (emphasis added). (62 Fed. Reg. 18937, at 18940 and 18943). This certainly means that methods other than publication of data are available to satisfy the requirement that the pivotal safety data be generally available.

<sup>5</sup> WHO Food Additives Series 35, Toxicological evaluation of certain food additives and contaminants; Prepared by the forty-fourth [1995] meeting of the Joint (FAO/WHO) Expert Committee on Food Additives (JECFA), pp 129-138. Copy provided as Appendix 9 to GRN 92.

<sup>6</sup> Much could be said regarding the adequacy of JECFA's toxicological monographs to support GRAS status, not only in terms of the expert consensus requirement but also the requirement that the safety data be generally available. In short, as FDA is aware through its own valuable participation with JECFA, the monographs contain a detailed description of the safety studies, numerical data on doses and outcome, the significance of each study to the safety evaluation, and analysis of metabolism and other studies. Data tables are presented if considered necessary. Clearly, the monographs are intended to provide the scientific community with the scientific studies and the scientific reasoning employed by JECFA. The JECFA review process is at least as reliable and informative as the ordinary peer review process that is typically required for scientific publication. Furthermore, JECFA's monographs provide a clear statement of the acceptable daily intake assigned to the reviewed substance; they are prepared by experts in the safety evaluation of food ingredients; and they present the relevant information in an easily followed format. Full reports of the safety studies are submitted to JECFA, and their quality is judged by JECFA's experts. This does not happen when a safety study is merely published in a peer-reviewed journal.

(continued ...)

nonetheless undertook to have a manuscript prepared, peer-reviewed, and accepted in a scientific journal. To require the manufacturer to wait until the article appears in print before GRAS status can be claimed is not justified in light of the totality of the circumstances present here.

Indeed, whether the article is actually published in February or April, 2002, we and FDA have every reason to expect that the article will be publicly available before the end of the normal review period for GRN 92. We note in this regard that it is not uncommon for FDA to respond favorably to a GRAS Notification 180 days or more after its receipt. In fact, according to the Agency's recently published CFSAN 2002 Program Priorities,<sup>7</sup> the Agency regards 180 days as a target for responding to GRAS Notifications. A 180-day review time for GRN 92 would correspond to a response letter dated June 5, 2002, based upon its submission date of December 5, 2001. As discussed below, there is ample precedent where the Agency has accepted GRAS submissions that relied upon pivotal data that did not yet appear in print at the time of the submission.

Considering the extremely strong case for safety and GRAS status presented in GRN 92, considering that the two-year study has been described in detail in a published JECFA monograph, and considering that the Agency does not rigidly apply the publication requirement in all GRAS determinations, it would have been appropriate to regard the public availability of data requirement as being sufficiently satisfied in the case of GRN 92. However, if the Agency were nonetheless concerned about the timing with which the two-year study would be publicly available, it might have waited to send the response letter only after the article appears in print, in keeping with its normal review time for GRAS Notifications.

#### *Time Gap Requirement*

Any requirement that published data be available for some period of time before they are used to support GRAS status can only be related to the expert consensus element of GRAS status. As clearly stated in the Notification, the expert consensus element in the case of this Notification is satisfied by, among other things, JECFA's favorable

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Certainly, FDA's apparent position that no JECFA toxicological monograph can satisfy the general availability of data requirement for GRAS status is not legally sound.

<sup>7</sup> CFSAN's priorities for 2002 are set forth in a document dated January 29, 2002, and published on the Agency's web site at: <http://www.cfsan.fda.gov/~dms/cfsa102b.html>. Regarding response time for GRAS Notifications, the document states as an objective "Complete processing of 80% of GRAS notifications (GRNs) in the receipt cohort of FY 2001 within 180 days."

evaluations of sucrose esters including its evaluation of the very two-year study in question. As FDA notes in the GRAS Notification proposal, "the basis for concluding that there is expert consensus historically has included publication in secondary sources, convening an expert panel, or relying on an opinion or recommendation of an authoritative body."<sup>8</sup> In this case, JECFA certainly qualifies as an authoritative body, and its conclusions certainly qualify as expert opinion. The study was completed in 1994 and evaluated by the 44th JECFA in 1995. JECFA describes the study in great detail in its 1995 toxicological monograph for sucrose esters presented as Appendix 9 to GRN 92. This monograph was published and reviewed by food safety experts. The authors and peer reviewers of the article prepared for publication further agree with its conclusions regarding the no-observed-effect-level (NOEL) demonstrated by the study. In short, there is little room to question whether a sufficient consensus exists among qualified experts that sucrose esters are safe, particularly at the low level of exposure covered by GRN 92. Therefore, leaving aside its validity, the Agency's rarely if ever asserted requirement that some period of time must pass between publication of the data and its use to support GRAS status is not appropriately applied in this case.

FDA has accepted GRAS determinations in the past that rely upon very recently published studies. An example is the Agency's response to McNeil Consumer Healthcare's February 18, 1999, submission regarding the GRAS status of stanol esters. McNeil's submission relied largely upon five studies that were published in the April, 1999, issue of *Regulatory Toxicology and Pharmacology*. In a letter dated May 17, 1999, the Agency responded favorably to McNeil's submission, stating that it had no questions regarding the GRAS determination. Similarly, in the case of GRN 19 (ferrous bisglycinate chelate) the pivotal safety data consisted of subchronic toxicity studies in rats. The GRAS Notification was submitted in April, 1999; the studies were published in July, 1999; and the Agency responded favorably in September, 1999. It is not possible to reconcile the Agency's no-objection letters to McNeil and to Albion Laboratories (GRN 19) with its response to GRN 92, specifically with regard to the timing of the publication of the pivotal data. Certainly, each GRAS Notification presents its own unique set of circumstances, and the Agency must engage in a case-by-case evaluation. However, both the stanol ester submission and GRN 19 sought to demonstrate GRAS status on the basis of scientific procedures, and GRAS status on the basis of scientific procedures requires that the pivotal safety data be generally available. We have no disagreement with the conclusions made by FDA in the case of stanol esters and GRN 19, and we understand that the Agency must have been influenced by the clear cases of safety made in those submissions. However, an equally clear or stronger case of safety was made in GRN 92, supported by the Agency's own ADI for sucrose esters, and an EDI many thousands of

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<sup>8</sup> 62 Fed. Reg. 18937 at 18943.

times less than the EDI presented in the stanol ester submission. In short, the Agency must either reverse its decision on GRN 92 or explain why the publication requirement and a time-gap requirement are applied strictly in some cases but not in others.

Finally, even if the time-gap requirement were applied in this case, it would be appropriate to recognize that the pivotal safety study was completed in 1994, and a sufficient amount of time has passed for its evaluation and assimilation by the scientific community, most notably the experts who participated in its evaluation at JECFA. A larger group of experts cannot realistically be expected to review critically and purposefully the article that has been prepared for publication.

#### *Defining the Pivotal Data*

It is often said that the "pivotal data" needed to support GRAS status must ordinarily be published.<sup>2</sup> FDA's February 4, 2002, letter wrongly finds fault with GRN 92 because "it is not clear to [FDA] that the body of evidence pertaining to sucrose fatty acid esters is publicly available." Mitsubishi cannot be asked to demonstrate that the entire body of evidence relating to the safety of sucrose esters be published in detail. An overwhelming body of evidence relating to the safety of sucrose esters is publicly available in the seven JECFA toxicological monographs included with GRN 92.

The 1994 two-year feeding study is the most extensive and up-to-date evaluation of the safety of sucrose esters. It represents significantly more safety information than is called for in FDA's Redbook to support the safety of sucrose esters in the described application. Sucrose esters, when introduced into the diet at roughly 0.5 mg/person/day, fall into the Redbook's Concern Level II, which does not call for a two-year animal feeding study. Given that a published two-year rat feeding study does exist, and given that this study forms the basis for JECFA's Acceptable Daily Intake assigned to sucrose esters (30 mg/kg body weight, or 1800 mg/person/day for a 60-kg individual), it is puzzling that FDA would dispute that this study more than adequately qualifies as pivotal data to support the GRAS status of sucrose esters in the described application.

The Agency's GRAS Notification proposal recognizes that, as with food additives, the quantity and quality of scientific evidence needed to support a safety evaluation for a GRAS substance will vary considerably depending upon factors such as the estimated dietary exposure, and the chemical, physical, and physiological properties

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<sup>2</sup> GRAS status based upon scientific procedures is "ordinarily based upon published studies, which may be corroborated by unpublished studies and other data and information." 21 C.F.R. § 170.30(b). The corroborative and/or unpublished data and information are generally regarded as less pivotal.

of the substance.<sup>10</sup> Thus, the amount of safety data and the amount of published safety data needed to support GRN 92 certainly does not include the entire body of evidence relating to sucrose ester safety.

FDA's letter notes that JECFA requested metabolic studies and a human tolerance study, suggesting that these studies may need to be publicly available before sucrose esters may be properly deemed GRAS. Without addressing this issue at length, JECFA was interested in the possibility of a laxative effect if sucrose esters are ingested at high doses. The well-conducted human tolerance study requested by JECFA showed no adverse effects in human volunteers at the highest dose level. The high-dose level was then used as a cap on the ADI derived from the two-year rat feeding study.<sup>11</sup> Under these circumstances, and particularly considering the extremely low dietary intake associated with GRN 92, the human tolerance study showing no adverse effects does not qualify as relevant data, much less pivotal data. Similarly, metabolic studies of the lower sucrose esters corroborate that they are mostly hydrolyzed to normal dietary constituents, sucrose and edible fatty acids, before absorption. This information is corroborative of their safety, but is not pivotal. In any event, GRN 92 cited a published article reporting on studies of the metabolism of sucrose esters in rat and man.<sup>12</sup> The remaining body of data need not be published in order to properly conclude that sucrose esters are GRAS for this application, involving such minuscule exposure.

Finally, a review of prior GRAS Notifications reveals many cases in which the Agency did not object to the publication of only one or two studies together with reliance on unpublished data. One example is GRN 56, which claimed GRAS status for diacylglycerol (DAG) oil. The safety data supporting that submission included published absorption and metabolism studies and *unpublished* acute, subchronic and chronic toxicity studies together with an *unpublished* mutagenicity study. The Notification also described *unpublished* clinical trials designed to study the effects of DAG on circulating lipid levels. Again, we have no disagreement with the Agency's no-objection response, but it stands in stark contrast to the Agency's assertion in the case of GRN 92 that a single published two-year toxicity study would not be adequate. In the case of GRN 92, clearly the most important study is published. In the case of GRN 56, FDA accepted the

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<sup>10</sup> 62 Fed. Reg. 18937 at 18942.

<sup>11</sup> WHO Food Additives Series 40, Toxicological evaluations of certain food additives and contaminants. Prepared by the forty-ninth [1997] meeting of the Joint (FAO/WHO) Expert Committee on Food Additives (JECFA), pp 79-81. Copy provided as Appendix 10 to GRN 92.

<sup>12</sup> Daniel and Marshall, "The Metabolism of Beef Tallow Sucrose Ester in Rat and Man" *Fd. Cosmet. Toxicol.* 17:19-21 (1979).

publication of a single study, and one that would appear to carry less significance than the body of unpublished studies.

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Our position might be summarized succinctly as follows: (1) sucrose esters are unquestionably safe in the application covered by GRN 92; (2) publication by JECFA of the two-year study, along with a substantial body of other information more than satisfies the general availability of data requirement; (3) the two-year study will appear in print within two months in a peer-reviewed journal and will also satisfy the general availability of data requirement; (4) JECFA's evaluations more than satisfy the expert consensus requirement and obviate the need for a time-gap before achievement of GRAS status; and (5) given that there is no question regarding safety, the Agency should not stretch for technical reasons to reject GRN 92. The effect of the Agency's response to GRN 92, if not reversed, is that Mitsubishi and FDA must devote additional resources to a resubmission of the Notification with no ensuing public health benefit. A second unfortunate effect of the Agency's response to GRN 92 is that it will discourage others from filing GRAS Notifications. These outcomes disagree sharply with the Agency's stated objectives behind the GRAS Notification proposal. The proposal was presented as a streamlining of the GRAS Affirmation Petition process, which would "allow FDA to redirect its resources to questions about GRAS status that are a priority with respect to public health protection."<sup>13</sup> FDA further noted that the GRAS Notification program would "provide an incentive for manufacturers to inform FDA of their GRAS determinations."<sup>14</sup> These stated objectives are reflected nowhere in the Agency's handling of GRN 92.

For all of these reasons, we respectfully request that the Agency reconsider and agree that GRN 92 provides a sufficient basis for our client to conclude that sucrose fatty acid esters are GRAS for the conditions of use described in GRN 92. If the Agency is unable to reach a decision promptly, please be advised that our client intends to resubmit its Notification immediately upon publication of the two-year rat feeding study.

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<sup>13</sup> 62 Fed. Reg. 18937 at 18941

<sup>14</sup> *id.*

Dr. Alan M. Rulis  
March 1, 2002  
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KELLER AND HECKMAN LLP

We appreciate your attention to the important issues raised in this letter and we look forward to your response.

Cordially yours,

John S. Eldred

David K. Joy

cc: Linda Kahl  
Paulette Gaynor

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