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Original Submission

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BELL, BOYD & LLOYD LLC

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OFFICES IN CHICAGO
AND WASHINGTON, D.C.

September 21, 2000

Office of Premarket Approval (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street SW
Washington, D.C. 20204

2000 SEP 25 P 2:08

Re: Conversion of GRAS Affirmation Petition on Gum Arabic, 3G2087
to GRAS Notification

Ladies and Gentlemen:

On behalf of our client, Kerry Ingredients, and pursuant to proposed § 170.36 of the agency's regulations, we respectfully request that the GRAS Affirmation Petition for gum arabic be converted to GRAS Notification.

In response to the specific requirements of proposed § 170.36 (g) (2), we respectfully submit the following:

(g)(2)(i) The name and address of the notifier

Kerry Ingredients
352 East Grand Avenue
Beloit, Wisconsin 53511

(g)(2)(ii) The applicable GRAS affirmation petition number

3G2087

(g)(2)(iii) The common or usual name of the substance that was the subject of the converted GRAS affirmation petition (i.e., the notified substance)

Gum Arabic

(g)(2)(iv) The applicable conditions of use of the notified substance that are supported by data and information in the referenced GRAS petition, including the foods in which the substance is to be used, levels of use in such foods, and the purposes for

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which the substance is used, including, when appropriate, a description of the population expected to consume the substance

(a) Information and reports on past uses in food

Gum arabic is affirmed as GRAS for use in many types of foods. 21 CFR § 184.1330. It was previously listed as GRAS in 21 CFR §§ 121.101(d)(7) published in 1961.

(b) Intended use levels of gum arabic in food

Gum arabic is intended for use as a thickener, emulsifier or stabilizer in the manufacture of creamers for use in manufacturing alcoholic beverages at levels not to exceed current good manufacturing practice. The level of use of gum arabic is to be limited to no more than 20% by weight of the alcoholic beverage. The population expected to consume gum arabic are those who drink alcoholic beverages.

(g)(2)(v) The basis for the GRAS determination (i.e., through scientific procedures or through experience based on common use in food)

The basis for GRAS determination is experience based on common use in food.

(g)(2)(vi) (A) A statement that the complete record that supports the GRAS determination has been submitted to the agency in the applicable GRAS petition; or

(B) A statement that the data and information that are the basis for the notifier's GRAS determination are available for FDA review and copying at reasonable times at a specific address set out in the claim or will be sent to FDA upon request.

The complete record that supports the GRAS determination has been submitted to the agency in the GRAS Affirmation Petition.

Respectfully submitted,

BELL, BOYD & LLOYD LLC

John F. Lemker

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Submission End

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BELL, BOYD & LLOYD LLC

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OFFICES IN CHICAGO
AND WASHINGTON, D.C.

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September 6, 2001

VIA OVERNIGHT DELIVERY

Robert I. Merker, Ph.D.
Food and Drug Administration
Office of Premarket Approval (HFS-206)
Center for Food Safety and
Applied Nutrition
1110 Vermont Ave., N.W.
Washington, DC 20201



RE: GRN 058/GRP 3G0287

Dear Dr. Merker:

In response to your communications of April 23, 2001 and August 20, 2001 regarding the most effective manner in which to process the above referenced petitions, Kerry, Inc. hereby requests that its GRAS Notification be converted to a Food Additive Petition. In conjunction with this request, Kerry claims a categorical exclusion from an environmental assessment under 21 C.F.R. § 25.32.(r).

Kerry, Inc., complies with the categorical exclusion in that the substance gum arabic occurs naturally in the environment and the approval of the petition will not alter significantly the concentration or distribution of the substance, its metabolic or degradation products in the environment.

To Kerry, Inc.'s knowledge no extraordinary circumstances exist which would require an Environmental Assessment.

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Robert I. Merker, Ph.D.
September 6, 2001
Page 2

Please contact me if you require any additional information. Thank you for your assistance.

Sincerely,

John F. Lemker

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

SEP 27 2001

Mr. John Lemker
 Bell, Boyd, and Lloyd LLC
 Three First National Plaza
 70 West Madison Street, Suite 3300
 Chicago, IL 60602-4207

Re: GRAS Notice No. GRN 000058

Dear Mr. Lemker:

The Food and Drug Administration (FDA) is responding to letters, dated September 21, 2000 and September 6, 2001, that you submitted on behalf of Kerry Ingredients (Kerry). Your September 21, 2000 letter requests that FDA convert the filed GRAS affirmation petition GRP 3G0287 to a GRAS notice in accordance with the agency's proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal). FDA received this conversion request on September 25, 2000 and designated it as GRAS Notice No. GRN 000058. In a series of telephone conversations, representatives of the Office of Food Additive Safety (OFAS) discussed your conversion request with you. In your letter dated September 6, 2001, you requested that FDA convert GRP 3G0287 to a food additive petition rather than continue to evaluate it as a GRAS notice. Given your request, FDA ceased to evaluate GRN 000058 on September 10, 2001, the date that we received your letter dated September 6, 2001.

GRP 3G0287 was submitted to FDA by Beatrice Foods, the business predecessor of Kerry Ingredients. The subject of GRP 3G0287 is gum arabic (acacia), which is the dried gummy exudate obtained from stems and branches of trees belonging to the various species of the genus *Acacia*. Different investigators have attributed 500 to 900 such species to this genus. The gum consists of the calcium, magnesium and potassium salts of arabic acid, an acid polysaccharide. The polysaccharide is a polymer that ranges from 250,000 to 1,000,000 in molecular weight. Its composition is approximately 30 percent L-arabinose, 37 percent D-galactose, 11 percent L-rhamnose, and 14 percent D-glucuronic acid.

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OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HFS-206	Kale	9/26/01	HFS-200	Ruhl	9-27-01			
HFS-206	Murphy	9/26/01						
HFS-205	Pank	9/26/01						

In GRP 3G0287, Kerry requests that FDA affirm that gum arabic is GRAS, through scientific procedures, for use as a thickener, emulsifier or stabilizer in the manufacture of creamers for use in manufacturing alcoholic beverages at a maximum level of use of 20 percent. Kerry relies on data and information discussed in a 1973 report of the Select Committee on GRAS substances (the Select Committee)¹ to support its view that the intended use of gum arabic in alcoholic beverages is GRAS (Ref. 1). In that 1973 report, the overall conclusion of the Select Committee was "[t]here is no evidence in the available information on gum arabic that demonstrates a hazard to the public when it is used at levels that are now current and in the manner now practiced. However, it is not possible to determine, without additional data, whether a significant increase in consumption would constitute a dietary hazard."

FDA has previously affirmed that gum arabic is GRAS for some uses at specified maximum levels of use (proposed rule, 39 FR 34204, September 23, 1974; final rule, 41 FR 53608, December 7, 1976; 21 CFR 184.1330). In large part, FDA based its affirmation of GRAS status on the 1973 report of the Select Committee in combination with the uses of gum arabic that manufacturers reported to the National Academy of Sciences/National Research Council in a comprehensive survey of the uses of various food ingredients.

In a rulemaking concurrent to the rulemaking that affirmed the GRAS status of some uses of gum arabic, FDA established 21 CFR 184.1(b)(2) (proposed rule, September 23, 1974, 39 FR 34194; final rule, December 7, 1976, 41 FR 53600). Under 21 CFR 184.1(b)(2), "[i]f the ingredient is affirmed as GRAS with specific limitation(s), it shall be used in food only within such limitation(s), including the category of food(s), the functional use(s) of the ingredient, and the level(s) of use. Any use of such an ingredient not in full compliance with each such established limitation shall require a food additive regulation." Subsequent to that rulemaking, FDA affirmed the GRAS status of a use of a food ingredient in accordance with 21 CFR 184.1(b)(2) when the Select Committee concluded "it is not possible to determine without additional data, whether a significant increase in consumption would constitute a dietary hazard." (See, e.g., 21 CFR 184.1097, 21 CFR 184.1115, 21 CFR 184.1115, and 21 CFR 184.1366). The Select Committee reached this conclusion in the case of gum arabic, and the rulemaking that affirmed the GRAS status of some uses of gum arabic makes clear that FDA viewed the regulation governing gum arabic within the same rubric as that of 21 CFR 184.1(b)(2) (see 39 FR 34194).

During the rulemaking that established 21 CFR 184.1(b)(2), FDA addressed a comment that contended that a subsequently instituted use that may in fact be GRAS would have to be covered by a food additive regulation. In response to this comment, FDA advised that 21 CFR 184.1(b)(2) does not require that a subsequent use be covered by a food additive regulation even though it may be GRAS. FDA specifically pointed out that a regulation affirming a substance as GRAS with specific limitations on the conditions of use may be amended to cover additional uses that have become GRAS. Importantly, either mechanism requires rulemaking - i.e., rulemaking that results in a food additive regulation or rulemaking that amends the current GRAS affirmation regulation.

¹During the 1970's, FDA initiated a comprehensive review of GRAS substances, including gum arabic. As part of the comprehensive review, FDA commissioned, through the Life Sciences Research Office of the Federation of American Societies for Experimental Biology, the "Select Committee on GRAS Substances." The charge to the Select Committee was to summarize the available scientific literature on certain substances and to provide a recommendation as to what restrictions, if any, on the use of each substance would be needed to ensure its safe use in food.

The rulemaking that affirmed the GRAS status of some uses of gum arabic, together with the rulemaking that established 21 CFR 184.1(b)(2), makes clear that the appropriate mechanism for Kerry to lawfully use gum arabic outside the limitations established in the existing regulation for gum arabic is to submit a petition to FDA. Kerry could petition FDA either to conduct rulemaking that results in a food additive regulation or to conduct rulemaking that amends the current GRAS affirmation regulation. Kerry did so when it submitted GRP 3G0287.

As discussed in the GRAS proposal, FDA is directing its resources to the food additive petition process, which is required by law, rather than to the GRAS affirmation petition process, which is voluntary. Given this fact, and given the regulatory framework that is associated with gum arabic, Kerry's letter dated September 6, 2001, requests that FDA convert GRP 3G0287 to a food additive petition. Because the agency already has devoted resources to the review of the data and information in GRP 3G0287, FDA expects to be able to process such a food additive petition promptly.

In accordance with proposed 21 CFR 170.36(f), a copy of the text of this letter, as well as a copy of the information in Kerry's notice that conforms to the information in proposed 21 CFR 170.36(c)(1), is available for public review and copying on the homepage of the Office of Food Additive Safety (on the Internet at <http://www.cfsan.fda.gov/~lrd/foodadd.html>).

Sincerely,

Alan M. Rulis, Ph.D.
Director
Office of Premarket Approval
Center for Food Safety
and Applied Nutrition

References

1. Life Sciences Research Office, Federation of American Societies for Experimental Biology. 1973. Evaluation of the Health Aspects of Gum Arabic as a Food Ingredient.

Hard copy cc: **GRN 000058 GRP 3G2087**

Electronic mail cc: GCF-1 (CCopp) HFS-200 (LTarantino) HFS-206 (LKahl)
HFS-205(GHPauli) HFS-215(PGaynor) HFS-830 (SAAnderson)
HFS-207(AMattia) HFS-246(MDiNovi)

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Filename: gn0058rl.wpd

R/D: HFS-206 (RIMerker):2/20/01; 9/14/01

Revised: LSKahl:HFS-206: 3/14/01; 4/4/01; 7/9/01; 9/18/01

Init: LSKahl: 9/18/01

MDiNovi: 9/19/01

GHPauli: 9/19/01

Revised per AMRulis: LSKahl: 9/26/01

F/T:HFS-206:September 26, 2001

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Mr. John Lemker
Bell, Boyd, and Lloyd LLC
Three First National Plaza
70 West Madison Street, Suite 3300
Chicago, IL 60602-4207

SEP 27 2001

Re: GRAS Notice No. GRN 000058

Dear Mr. Lemker:

The Food and Drug Administration (FDA) is responding to letters, dated September 21, 2000 and September 6, 2001, that you submitted on behalf of Kerry Ingredients (Kerry). Your September 21, 2000 letter requests that FDA convert the filed GRAS affirmation petition GRP 3G0287 to a GRAS notice in accordance with the agency's proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal). FDA received this conversion request on September 25, 2000 and designated it as GRAS Notice No. GRN 000058. In a series of telephone conversations, representatives of the Office of Food Additive Safety (OFAS) discussed your conversion request with you. In your letter dated September 6, 2001, you requested that FDA convert GRP 3G0287 to a food additive petition rather than continue to evaluate it as a GRAS notice. Given your request, FDA ceased to evaluate GRN-000058 on September 10, 2001, the date that we received your letter dated September 6, 2001.

GRP 3G0287 was submitted to FDA by Beatrice Foods, the business predecessor of Kerry Ingredients. The subject of GRP 3G0287 is gum arabic (acacia), which is the dried gummy exudate obtained from stems and branches of trees belonging to the various species of the genus *Acacia*. Different investigators have attributed 500 to 900 such species to this genus. The gum consists of the calcium, magnesium and potassium salts of arabic acid, an acid polysaccharide. The polysaccharide is a polymer that ranges from 250,000 to 1,000,000 in molecular weight. Its composition is approximately 30 percent L-arabinose, 37 percent D-galactose, 11 percent L-rhamnose, and 14 percent D-glucuronic acid.

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In GRP 3G0287, Kerry requests that FDA affirm that gum arabic is GRAS, through scientific procedures, for use as a thickener, emulsifier or stabilizer in the manufacture of creamers for use in manufacturing alcoholic beverages at a maximum level of use of 20 percent. Kerry relies on data and information discussed in a 1973 report of the Select Committee on GRAS substances (the Select Committee)¹ to support its view that the intended use of gum arabic in alcoholic beverages is GRAS (Ref. 1). In that 1973 report, the overall conclusion of the Select Committee was "[t]here is no evidence in the available information on gum arabic that demonstrates a hazard to the public when it is used at levels that are now current and in the manner now practiced. However, it is not possible to determine, without additional data, whether a significant increase in consumption would constitute a dietary hazard."

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results in a food additive regulation or rulemaking that amends the current GRAS affirmation regulation.

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Sincerely,

Alan M. Rulis, Ph.D.
Director
Office of Premarket Approval
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References

1. Life Sciences Research Office, Federation of American Societies for Experimental Biology. 1973. Evaluation of the Health Aspects of Gum Arabic as a Food Ingredient.

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Pages 000017- 000048 have been removed in accordance with copyright laws. Please see appended bibliography list of the references that have been removed from this request.

above office during working hours, Monday through Friday.

Dated: September 9, 1974.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

NOTE: Incorporation by reference provisions approved by the Director of the Office of the Federal Register July 10, 1973.

[FR Doc.74-21197 Filed 9-20-74; 8:45 am]

[21 CFR Part 121]
GUM ARABIC (ACACIA)

Proposed Affirmation of GRAS Status With Specific Limitations as Direct Human Food Ingredient and Affirmation of GRAS Status as Indirect Human Food Ingredient

The Food and Drug Administration is conducting a comprehensive study of direct human food ingredients classified as generally recognized as safe (GRAS) or subject to a prior sanction. The Commissioner of Food and Drugs has issued several notices and proposed regulations, published in the FEDERAL REGISTER of July 26, 1973 (38 FR 20035-20057), implementing this review. Elsewhere in this issue of the FEDERAL REGISTER, the Commissioner is issuing the final regulations resulting from those proposals. Pursuant to this review, the safety of gum arabic has been evaluated. In accordance with the provisions of § 121.40, the Commissioner proposes to affirm the direct use of gum arabic in food as GRAS with specific limitations, and to affirm its GRAS status for use in food-contact articles.

Gum arabic (acacia) is listed in § 121.101(d) (7), published in the FEDERAL REGISTER of January 31, 1961 (26 FR 938), as GRAS as a food stabilizer; and in § 121.101(i), published in the FEDERAL REGISTER of June 10, 1961 (26 FR 5224), as GRAS for substances migrating from cotton and cotton fabrics used in dry food packaging. Gum arabic is the dried, gummy exudate obtained from stems and branches of trees belonging to the various species of the genus *Acacia*. The number of species of the genus *Acacia* has been estimated by various investigators at from 500 to 900. Almost all of the gum used in the United States is imported from the Sudan Republic and is obtained from *Acacia senegal* Linne. Analysis shows this gum to be the calcium, magnesium, and potassium salts of a polysaccharide acid, arabic acid. It is composed of about 30 percent L-arabinose, 37 percent D-galactose, 11 percent L-rhamnose and 14 percent glucuronic acid. The molecular weight is believed to vary from about 250,000 to 1,000,000.

Gum arabic has been the subject of a search of the scientific literature from 1920 to the present. The parameters used in the search were chosen to discover any articles that considered (1) the chemical toxicity, (2) occupational hazards, (3) metabolism, (4) reaction products, (5) degradation products, (6) any reported carcinogenicity, teratogenicity or mutagenicity, (7) dose response, (8)

reproductive effects, (9) histology, (10) embryology, (11) behavioral effects, (12) detection, and (13) processing. A total of 388 abstracts on gum arabic was reviewed and 45 particularly pertinent reports from the literature survey have been summarized in a Scientific Literature Review.

Gum arabic is probably the oldest and best known of the vegetable gums, reported to be first used in the United States in 1880. A representative cross-section of food manufacturers was surveyed to determine the specific foods in which gum arabic was used and at what levels. Available surveys of consumer consumption were obtained and combined with the production information to obtain an estimate of the consumer exposure to gum arabic. The total poundage of gum arabic used by the U.S. food industry in 1970 was 10.4 million pounds, about three times that used in 1960.

The Scientific Literature Review shows, among other studies, the following information as summarized in the report of the Select Committee on GRAS Substances (SCOGS):

ABSORPTION AND METABOLISM

The available information does not establish clearly the fate of ingested gum arabic. In one study, rats were fed for one week on a basal ration supplemented with various levels of gum arabic. Using a method involving restricted food and caloric intakes, gum arabic fed to weanling male Sprague-Dawley rats at dietary levels of 0.5 g per day and 2 g per day was shown to have caloric values of 131 percent and 110 percent of corn starch, respectively. In a similar study, gum arabic fed to weanling rats, at a level of 1 g per day was shown to have a caloric value 75 percent that of sucrose. While both of these studies suggest absorption of gum arabic or some digestion product, an earlier study did not support these observations. Using a test for glycogenesis rats were fed high levels (34 percent gum arabic) in a single meal. Seventy-two hours later hepatic glycogen levels were determined. It was concluded that the difference in liver glycogen between the control and gum-fed rats was insignificant.

As in the rat, the guinea pig appears to have some ability to utilize gum arabic for energy. Two feeding studies have indicated that gum arabic exhibits growth-promoting effects. In one study, 89 to 95 percent digestibility was reported, while in the other, about 70-80 percent of normal growth rate was reported and the investigators appeared to emphasize the need for the intact gum molecule.

The rabbit also appears to be able to utilize gum arabic. A total caloric value for gum arabic slightly greater than that for starch has been reported. In the same study, evidence for glycogenesis was demonstrated.

In one study with humans, no evidence for absorption of the intact gum molecule was found. In this study, 22 infants 1 to 15 months old were fed 15 to 20 g per day of gum arabic in milk. No urinary pentose excretion was observed, while significant excretion of gum arabic occurred in the stools.

It would appear, then, that gum arabic is capable of being digested to simple sugars in herbivores, and to some extent in omnivores such as man. After absorption, the digestion products are available for oxidation. Conclusive evidence indicating that the intact gum arabic molecule is absorbed under normal conditions is lacking.

SHORT TERM STUDIES

Several short term feeding studies have been made with laboratory animals. In one, guinea pigs were fed a synthetic diet for 6 weeks and the effects of various supplements were noted. The animals on a gum arabic supplement showed a slightly lower growth rate than did the control animals. Similar results were obtained in a succeeding study in which the effects of various mineral supplements were noted. In both studies it appears that the basal ration was deficient in some way. In spite of this, gum arabic tended to improve growth rate. When the influence of feeding gum arabic on the intestinal synthesis of vitamin B₁₂ was examined, it was shown not only to permit growth in guinea pig but also to promote the intestinal synthesis of the vitamin. In rabbits the ingestion of diets providing 20 percent by weight of gum arabic permitted significant growth with no evidence of deleterious effects.

Studies in mice, rats, hamsters, and rabbits showed no clearly discernible teratological effects with oral doses of gum arabic up to 1,600 mg per kg per day in mice, rats, and hamsters, and up to 37 mg per kg per day in rabbits, when each animal was treated daily for 10 days (5 days in hamsters and 13 days in rabbits), starting at the sixth day of gestation. However, at a dose level of 800 mg per kg per day in rabbits, a majority of the dams died.

No mutagenic effect was noted in the recombination frequency in a host-mediated assay in mice, and no mutagenic effects were noted in a dominant lethal gene test in rats. However, a moderate effect was observed in the cytogenetic effect assay in bone marrow after in vivo treatment with 5.0 g per kg and 2.5 g per kg in rats. In general, these represented chromosomal breaks rather than recombinations and occurred within 6 hours after treatment. Similar effects were found in in vitro tissue cultures of human embryonic lung cells.

Neither oral LD₅₀ values nor long term gum arabic feeding studies have been reported.

OTHER STUDIES

There are several reports on the effect of parenterally administered gum arabic in man and other animals.

Treatment with intraperitoneal doses of gum arabic three times per week for up to 15 weeks in rats revealed no evidence of carcinogenicity. Solutions in saline or water containing 1.75 or 7.00 percent gum arabic were used. The size of dose is difficult to ascertain from the data presented, but it appears that levels were of the order of several hundred mg per kg. In a similar study with mice, no carcinogenic effect was noted, but amounts of gum arabic injected are not indicated. Injections of as much as 4.8 g of gum arabic per kg in dogs elicited no evidence of toxic effects but the same dose level killed dehydrated dogs, the highest no effect level being 1.9 g per kg.

The intravenous LD₅₀ of sodium arabinat, specially prepared from calcium arabinat by alcohol precipitation from an aqueous sodium chloride solution, can be estimated as 1 g per kg in rabbits from data reported. The effect of single and repeated intravenous doses of gum arabic solution in dogs was investigated. Total doses ranged from about 1 to 2 g per kg given over a period ranging from 1 to 84 days. The most characteristic finding was that of enlarged livers and swollen kidneys. Similar levels of gum arabic were fatal to two rabbits.

A similar study in which doses ranging from 16 to 48 g per kg were given intravenously over 76 days to three dogs showed gum arabic to be stored in the liver for as much as

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above office during working hours, Monday through Friday.

Dated: September 9, 1974.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

NOTE: Incorporation by reference provisions approved by the Director of the Office of the Federal Register July 10, 1973.

[FR Doc.74-21197 Filed 9-20-74;8:45 am]

[21 CFR Part 121]

GUM ARABIC (ACACIA)

Proposed Affirmation of GRAS Status With Specific Limitations as Direct Human Food Ingredient and Affirmation of GRAS Status as Indirect Human Food Ingredient

The Food and Drug Administration is conducting a comprehensive study of direct human food ingredients classified as generally recognized as safe (GRAS) or subject to a prior sanction. The Commissioner of Food and Drugs has issued several notices and proposed regulations, published in the FEDERAL REGISTER of July 26, 1973 (38 FR 20035-20057), implementing this review. Elsewhere in this issue of the FEDERAL REGISTER, the Commissioner is issuing the final regulations resulting from those proposals. Pursuant to this review, the safety of gum arabic has been evaluated. In accordance with the provisions of § 121.40, the Commissioner proposes to affirm the direct use of gum arabic in food as GRAS with specific limitations, and to affirm its GRAS status for use in food-contact articles.

Gum arabic (acacia) is listed in § 121.101(d) (7), published in the FEDERAL REGISTER of January 31, 1961 (26 FR 938), as GRAS as a food stabilizer; and in § 121.101(i), published in the FEDERAL REGISTER of June 10, 1961 (26 FR 5224), as GRAS for substances migrating from cotton and cotton fabrics used in dry food packaging. Gum arabic is the dried, gummy exudate obtained from stems and branches of trees belonging to the various species of the genus *Acacia*. The number of species of the genus *Acacia* has been estimated by various investigators at from 500 to 900. Almost all of the gum used in the United States is imported from the Sudan Republic and is obtained from *Acacia senegal* Linne. Analysis shows this gum to be the calcium, magnesium, and potassium salts of a polysaccharide acid, arabic acid. It is composed of about 30 percent L-arabinose, 37 percent D-galactose, 11 percent L-rhamnose and 14 percent glucuronic acid. The molecular weight is believed to vary from about 250,000 to 1,000,000.

Gum arabic has been the subject of a search of the scientific literature from 1820 to the present. The parameters used in the search were chosen to discover any articles that considered (1) the chemical toxicity, (2) occupational hazards, (3) metabolism, (4) reaction products, (5) degradation products, (6) any reported carcinogenicity, teratogenicity or mutagenicity, (7) dose response, (8)

reproductive effects, (9) histology, (10) embryology, (11) behavioral effects, (12) detection, and (13) processing. A total of 388 abstracts on gum arabic was reviewed and 45 particularly pertinent reports from the literature survey have been summarized in a Scientific Literature Review.

Gum arabic is probably the oldest and best known of the vegetable gums, reported to be first used in the United States in 1880. A representative cross-section of food manufacturers was surveyed to determine the specific foods in which gum arabic was used and at what levels. Available surveys of consumer consumption were obtained and combined with the production information to obtain an estimate of the consumer exposure to gum arabic. The total poundage of gum arabic used by the U.S. food industry in 1970 was 10.4 million pounds, about three times that used in 1960.

The Scientific Literature Review shows, among other studies, the following information as summarized in the report of the Select Committee on GRAS Substances (SCOGS):

ABSORPTION AND METABOLISM

The available information does not establish clearly the fate of ingested gum arabic. In one study, rats were fed for one week on a basal ration supplemented with various levels of gum arabic. Using a method involving restricted food and caloric intakes, gum arabic fed to weanling male Sprague-Dawley rats at dietary levels of 0.5 g per day and 2 g per day was shown to have caloric values of 131 percent and 110 percent of corn starch, respectively. In a similar study, gum arabic fed to weanling rats, at a level of 1 g per day was shown to have a caloric value 75 percent that of sucrose. While both of these studies suggest absorption of gum arabic or some digestion product, an earlier study did not support these observations. Using a test for glycogenesis rats were fed high levels (34 percent gum arabic) in a single meal. Seventy-two hours later hepatic glycogen levels were determined. It was concluded that the difference in liver glycogen between the control and gum-fed rats was insignificant.

As in the rat, the guinea pig appears to have some ability to utilize gum arabic for energy. Two feeding studies have indicated that gum arabic exhibits growth-promoting effects. In one study, 89 to 95 percent digestibility was reported, while in the other, about 70-80 percent of normal growth rate was reported and the investigators appeared to emphasize the need for the intact gum molecule.

The rabbit also appears to be able to utilize gum arabic. A total caloric value for gum arabic slightly greater than that for starch has been reported. In the same study, evidence for glycogenesis was demonstrated.

In one study with humans, no evidence for absorption of the intact gum molecule was found. In this study, 22 infants 1 to 15 months old were fed 15 to 20 g per day of gum arabic in milk. No urinary pentose excretion was observed, while significant excretion of gum arabic occurred in the stools.

It would appear, then, that gum arabic is capable of being digested to simple sugars in herbivores, and to some extent in omnivores such as man. After absorption, the digestion products are available for oxidation. Conclusive evidence indicating that the intact gum arabic molecule is absorbed under normal conditions is lacking.

SHORT TERM STUDIES

Several short term feeding studies have been made with laboratory animals. In one, guinea pigs were fed a synthetic diet for 6 weeks and the effects of various supplements were noted. The animals on a gum arabic supplement showed a slightly lower growth rate than did the control animals. Similar results were obtained in a succeeding study in which the effects of various mineral supplements were noted. In both studies it appears that the basal ration was deficient in some way. In spite of this, gum arabic tended to improve growth rate. When the influence of feeding gum arabic on the intestinal synthesis of vitamin B₁₂ was examined, it was shown not only to permit growth in guinea pig but also to promote the intestinal synthesis of the vitamin. In rabbits the ingestion of diets providing 20 percent by weight of gum arabic permitted significant growth with no evidence of deleterious effects.

Studies in mice, rats, hamsters, and rabbits showed no clearly discernible teratological effects with oral doses of gum arabic up to 1,600 mg per kg per day in mice, rats, and hamsters, and up to 37 mg per kg per day in rabbits, when each animal was treated daily for 10 days (5 days in hamsters and 13 days in rabbits), starting at the sixth day of gestation. However, at a dose level of 800 mg per kg per day in rabbits, a majority of the dams died.

No mutagenic effect was noted in the recombination frequency in a host-mediated assay in mice, and no mutagenic effects were noted in a dominant lethal gene test in rats. However, a moderate effect was observed in the cytogenetic effect assay in bone marrow after in vivo treatment with 5.0 g per kg and 2.5 g per kg in rats. In general, these represented chromosomal breaks rather than recombinations and occurred within 6 hours after treatment. Similar effects were found in in vitro tissue cultures of human embryonic lung cells.

Neither oral LD₅₀ values nor long term gum arabic feeding studies have been reported.

OTHER STUDIES

There are several reports on the effect of parenterally administered gum arabic in man and other animals.

Treatment with intraperitoneal doses of gum arabic three times per week for up to 15 weeks in rats revealed no evidence of carcinogenicity. Solutions in saline or water containing 1.75 or 7.00 percent gum arabic were used. The size of dose is difficult to ascertain from the data presented, but it appears that levels were of the order of several hundred mg per kg. In a similar study with mice, no carcinogenic effect was noted, but amounts of gum arabic injected are not indicated. Injections of as much as 4.8 g of gum arabic per kg in dogs elicited no evidence of toxic effects but the same dose level killed dehydrated dogs, the highest no effect level being 1.9 g per kg.

The intravenous LD₅₀ of sodium arabinat, specially prepared from calcium arabinat by alcohol precipitation from an aqueous sodium chloride solution, can be estimated as 1 g per kg in rabbits from data reported. The effect of single and repeated intravenous doses of gum arabic solution in dogs was investigated. Total doses ranged from about 1 to 2 g per kg given over a period ranging from 1 to 84 days. The most characteristic finding was that of enlarged livers and swollen kidneys. Similar levels of gum arabic were fatal to two rabbits.

A similar study in which doses ranging from 16 to 48 g per kg were given intravenously over 76 days to three dogs showed gum arabic to be stored in the liver for as much as

2 years after cessation of dosing in the two dogs that survived. The dog administered gum arabic at the level of 48 g per kg died 6 months after cessation of the treatment. No functional hepatic injury was noted, but amounts of gum arabic were found in liver.

Hospitalized patients have received gum arabic solutions intravenously as a part of therapy in an attempt to develop a blood plasma substitute in the treatment of shock. These early trials conducted between 1922 and 1937 proved unsuccessful. They do provide an estimate of the intravenous acute toxicity of this relatively crude substance for man to be of the order of 150 to 600 mg per kg.

Other human studies on patients with nephrosis, as well as studies on dogs and rabbits, showed that intravenously injected gum arabic or some product associated with it accumulated in the liver and remained in the tissues for several months. Non-lethal effects included serious disturbances in hemoglobin, white blood cells, and serum proteins. These investigators also noted that in the nephrotic patient about 20 percent of the gum arabic injected over a period of 8 weeks was excreted in the urine. Similar accumulation effects have been noted in other animal studies. Studies have also been reported to indicate the mobilization of gum arabic from storage in various organs.

These observations become more important when considered in terms of the possible oral allergenicity of gum arabic. Studies in animals have shown that the antigenic property of the gum is a function of the gum itself and not of a contaminant. Other studies have confirmed that sensitivity to gum arabic is in fact a true antibody-antigen phenomenon and not an artifact of some other metabolic event. Human sensitivity to gum arabic has been suggested in a number of reports of work-associated allergic reactions to the gum. However, the most carefully documented series of studies on human subjects and their response to oral administration of vegetable gums in general and gum arabic in particular is that of Gelfand. In 10 sensitive patients, vegetable gums in their food were confirmed as the allergens responsible for their sensitivity. Moreover, Gelfand was also able to show cross-sensitivity with several other gums such as tragacanth and karaya.

In general, the foregoing studies suggest a systemic effect of gum arabic when administered intravenously. Moreover, there appears to be in certain susceptible individuals significant allergic response to ingestion of this gum.

All of the available safety information on gum arabic has been carefully evaluated by qualified scientists of the Select Committee on GRAS Substances selected by the Life Sciences Research Office of the Federation of American Societies for Experimental Biology (FASEB). It is the opinion of the Select Committee that:

In common with many other food ingredients of natural origin, commercial gum arabic is a relatively crude and undefined material. In view of the demonstrated capacity of this material as a sensitizing agent, and despite strong indications that sensitization is due to the gum polysaccharide itself, it becomes important to know, nevertheless, to what extent extraneous contaminants such as protein may be contained in the commercial product. The Select Commit-

tee suggests consideration of revising the specifications for gum arabic to establish limits for the content of materials such as protein that may possibly be associated with some of the observed biological effects of the commercial gum.

In view of the prevalence of allergies to gum arabic, and its increasing use in a wide variety of food products, additional experiments should be undertaken to evaluate the significance of its allergenicity in the population as a whole. An epidemiological survey might determine whether significant numbers of persons are being placed in a state of receptiveness to cross-reactive allergies based upon daily lifelong exposures to gum arabic and two other gums alleged to be allergenic, gum tragacanth and karaya gum.

Gum arabic, fed at relatively high levels, is reported to be toxic to pregnant animals of one species. Hence it may be advisable, in due course, to conduct feeding studies in several animal species, including pregnant animals, at dosage levels that approximate and exceed the current maximum daily human intake.

It is the conclusion of the Select Committee that there is no evidence in the available information on gum arabic that demonstrates a hazard to the public when it is used at current levels and in the manner now practiced, but not necessarily under different conditions of use. It is not possible to determine, without additional data, whether a significant increase in consumption would constitute a dietary hazard. Based on his own evaluation of all available information on gum arabic, the Commissioner concurs with this conclusion. The Commissioner therefore concludes that continued safe use of gum arabic requires regulation of this GRAS ingredient with specific limitations to preserve present conditions of use. The levels of use adopted in this proposal, for various categories of food, are the maximum levels reported to the National Academy of Sciences/National Research Council in their survey of food manufacturers. Use of the ingredient in any manner not permitted by the proposed regulation results in its becoming a food additive for which no regulation currently exists.

The Commissioner, in reaching this conclusion, recognizes that many substances occurring in nature may produce allergic type reactions in susceptible individuals. As an indication of the large variety of materials which have been implicated, there can be mentioned dusts of various kinds, pollens, feathers, seeds, dandruff, and foods. In general, sensitive individuals may react with a number of responses which may include, among others, angioedema, urticaria, bronchial asthma, pruritis, and vascular purpura. In some instances, these reactions may be life threatening. Within the past several decades there has accumulated a body of evidence which indicates that food ingredients may indeed produce sensitization in susceptible individuals, and these include gum tragacanth, gum arabic, and sterculia (karaya) gum. However, the data on these gums do not suggest an incidence of reactions sufficiently

greater than those produced by other foods, to justify a conclusion at this time that they are not GRAS.

The Food and Drug Administration has been concerned about allergies, involving cosmetics and drugs, as well as food ingredients, and concurs with the suggestion of the Select Committee that a survey of the allergenic effects of tragacanth, arabic, and sterculia gums is needed. However, such a study should consider more than these three gums.

Funds of approximately \$250,000 have been provided for this fiscal year to contract for information on how to predict human intolerances to food ingredients, and an analysis of human intolerance case histories. The results of these contracts should provide the agency with the necessary information to channel resources to minimize allergic reactions from food to the degree possible.

Meanwhile, the Commissioner is of the opinion that the particular gums used should be specifically named on the labels of all foods. Proposals to amend certain food standards to require the naming of the specific gum(s) used are in process and will be published in the future.

Copies of the Scientific Literature Review on gum arabic, reports of the teratology and mutagenic screening tests for the ingredient, and the report of the Select Committee are available for review at the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852, and may be purchased from the National Technical Information Service (NTIS), 5285 Port Royal Rd., Springfield, VA 22151, as follows:

Title	Order number	Cost
Gum arabic (scientific literature review).	PB-221-201	\$4.85
Gum arabic (teratology tests)	PB-221-796	4.50
Gum arabic (mutagenic tests)	PB-221-821	5.45
Gum arabic (FASEB evaluation).	FDABF-GRAS-207	3.00

The above titles may also be purchased in microfiche form. Microfiche document prices are \$1.45 each for those with order numbers having an FDABF prefix or AS suffix, and \$0.95 each for all others.

This proposed action does not affect the present use of gum arabic for pet food or animal feed.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409, 701(a), 52 Stat. 1055, 72 Stat. 1784-1788 as amended; 21 U.S.C. 321(s), 348, 371(a)) and under authority delegated to him (21 CFR 2.120), the Commissioner proposes that Part 121 be amended as follows:

1. In § 121.101(d)(7) by revising the entry for "Acacia (gum arabic)" to read as follows:

§ 121.101 Substances that are generally recognized as safe.

(d) * * *

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PROPOSED RULES

Product	Tolerance	Limitations, restrictions, or explanations
* * *	* * *	* * *
(7) STABILIZERS		
Acacia (gum arabic).....		Affirmed as GRAS, § 121.104(g)(19); affirmed as GRAS for food-contact surfaces, § 121.105(f)(4).
* * *	* * *	

2. In § 121.104 by adding a new paragraph (g) (19) to read as follows:

§ 121.104 Substances added directly to human food affirmed as generally recognized as safe (GRAS).

(g) * * *

(19) *Gum arabic*. (i) Gum arabic is the dried gummy exudate from stems and branches of trees of various species of

the genus *Acacia*, family Leguminosae.
 (ii) The ingredient meets specifications of the Food Chemicals Codex, 2d Ed. (1972).¹
 (iii) The ingredient is used in food under the following conditions:

¹Copies may be obtained from: National Academy of Sciences, 2101 Constitution Ave. NW., Washington, DC 20037.

MAXIMUM USAGE LEVELS PERMITTED

Food categories	Percent	Function
Chewing gum, § 121.1(n)(6).....	5.6	Flavoring agent and adjunct, § 121.1(o)(12); formulation aid, § 121.1(o)(14); humectant, § 121.1(o)(16); surface-finishing agent, § 121.1(o)(30).
Confections and frostings, § 121.1(n)(9).....	12.4	Formulation aid, § 121.1(o)(14); stabilizer and thickener, § 121.1(o)(28); surface-finishing agent, § 121.1(o)(30).
Dairy product analogs, § 121.1(n)(10).....	1.3	Stabilizer and thickener, § 121.1(o)(28).
Fats and oils § 121.1(n)(12).....	1.5	Stabilizer and thickener, § 121.1(o)(28).
Hard candy and cough drops, § 121.1(n)(25).....	31.0	Flavoring agent and adjunct, § 121.1(o)(12); formulation aid, § 121.1(o)(14).
Snack foods, § 121.1(n)(37).....	2.9	Emulsifier and emulsifier salt, § 121.1(o)(8).
Nuts and nut products, § 121.1(n)(32).....	8.3	Formulation aid, § 121.1(o)(14); surface-finishing agent, § 121.1(o)(30).
Soft candy, § 121.1(n)(38).....	85.0	Emulsifier and emulsifier salt, § 121.1(o)(8); firming agent, § 121.1(o)(10); flavoring agent and adjunct, § 121.1(o)(12); formulation aid, § 121.1(o)(14); humectant, § 121.1(o)(16); stabilizer and thickener, § 121.1(o)(28); surface-finishing agent, § 121.1(o)(30).
All other food categories.....	1.0	Emulsifier and emulsifier salt, § 121.1(o)(8); flavoring agent and adjunct, § 121.1(o)(12); formulation aid, § 121.1(o)(14); stabilizer and thickener; § 121.1(o)(28).

3. In § 121.105 by adding a new paragraph (f) (4) to read as follows:

§ 121.105 Substances in food contact surfaces affirmed as generally recognized as safe (GRAS).

(f) * * *

(4) *Gum arabic*. (i) Gum arabic is the dried gummy exudate from stems and branches of trees of various species of the genus *Acacia*, family Leguminosae.

(ii) The ingredient meets specifications of the Food Chemicals Codex, 2d Ed. (1972).¹

(iii) The ingredient is used or intended for use as a constituent of food packaging containers.

(iv) The ingredient is used at levels not to exceed good manufacturing practices.

The Commissioner hereby gives notice that he is unaware of any prior sanction for the use of this ingredient in food under conditions different from those proposed herein. Any person who intends to assert or rely on such a sanction shall submit proof of its existence in response to this proposal. The regulation proposed above will constitute a determination that excluded uses would result in adulteration of the food in violation of section 402 of the act, and the failure of any person to come forward with proof of such an applicable prior sanction in response to this proposal constitutes a waiver of the right to assert or rely on

sanction at any later time. This notice also constitutes a proposal to establish a regulation under Subpart E, incorporating the same provisions, in the event that such a regulation is determined to be appropriate as a result of submission of proof of such an applicable prior sanction in response to this proposal.

Interested persons may, on or before December 23, 1974, file with the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852, written comments (preferably in quintuplicate) regarding this proposal. Comments may be accompanied by a memorandum or brief in support thereof. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: September 9, 1974.

A. M. SCHMIDT,
 Commissioner of Food and Drugs.

NOTE: Incorporation by reference provisions approved by the Director of the Office of the Federal Register July 10, 1973.

[FR Doc.74-21196 Filed 9-20-74; 8:45 am]

[21 CFR Part 121]

GUM GHATTI

Proposed Affirmation of GRAS Status With Specific Limitations as Direct Human Food Ingredient

The Food and Drug Administration is conducting a comprehensive study of

direct human food ingredients classified as generally recognized as safe (GRAS) or subject to a prior sanction. The Commissioner of Food and Drugs has issued several notices and proposed regulations, published in the FEDERAL REGISTER of July 26, 1973 (38 FR 20035-20057), implementing this review. Elsewhere in this issue of the FEDERAL REGISTER, the Commissioner is issuing the final regulations resulting from those proposals. Pursuant to this review, the safety of gum ghatti has been evaluated. In accordance with the provisions of § 121.40, the Commissioner proposes to affirm the direct use of gum ghatti in food as GRAS with specific limitations.

Gum ghatti, or Indian gum, has been listed in § 121.101(d)(7), published in the FEDERAL REGISTER of January 31, 1961 (26 FR 938), as GRAS as a food stabilizer. Gum ghatti is obtained as an exudate from wounds in the bark of *Anogeissus latifolia*, a large tree in the dry deciduous forests of India and Ceylon. The gum is basically the calcium salt of ghatti acid, a complex polysaccharide whose exact chemical structure is obscure and has not been determined. The dried gum has considerable nonfood use, primarily in oil-drilling muds, and is also used in drugs and cosmetics. Other parts of the tree from which this exudate is obtained have no reported human food or food ingredient uses. This proposal covers only the gum whose food ingredient uses began as early as 1938 in the United States.

Gum ghatti has been the subject of a search of the scientific literature from 1920 to the present. The parameters used in the search were chosen to discover any articles that considered (1) chemical toxicity, (2) occupational hazards, (3) metabolism, (4) reaction products, (5) degradation products, (6) any reported carcinogenicity, teratogenicity or mutagenicity, (7) dose response, (8) reproductive effects, (9) histology, (10) embryology, (11) behavioral effects, (12) detection, and (13) processing. A total of 19 abstracts on gum ghatti was reviewed and 9 particularly pertinent reports from the literature survey have been summarized in a Scientific Literature Review.

A representative cross-section of food manufacturers was surveyed to determine the specific foods in which gum ghatti was used and at what levels. Available surveys of consumer consumption were obtained and combined with the production information to obtain an estimate of the consumer exposure to gum ghatti. The total gum ghatti used in food in 1970 is reported to be a little more than 4,000 pounds. No data or information on use in prior years is available.

The Scientific Literature Review shows, among other studies, the following information as summarized in the report of the Select Committee on GRAS Substances (SCOGS):

Very little biological and toxicological data are available on gum ghatti in animals or man. Nothing is known about the absorption, distribution, metabolism or excretion of the gum in man or in animals and no short term or long term feeding experiments in laboratory animals have been reported.

DEPARTMENT OF HEALTH,
EDUCATION, AND WELFARE
Food and Drug Administration

[21 CFR Part 121]

GENERAL RECOGNITION OF SAFETY AND
PRIOR SANCTIONS FOR FOOD INGREDIENTS

Notice of Proposed Rule Making

In the FEDERAL REGISTER of July 26, 1973 (38 FR 20035-20057), the Commissioner of Food and Drugs issued several proposed regulations and notices governing the review of the safety of ingredients that have been used in food on the determination that they are generally recognized as safe (GRAS) or subject to a prior sanction from the Food and Drug Administration or the United States Department of Agriculture issued prior to September 6, 1958, the effective date of section 201(s) of the Federal Food, Drug, and Cosmetic Act. The Commissioner had promulgated definitions in § 121.1 (21 CFR 121.1), criteria for determining GRAS status in § 121.3 (21 CFR 121.3), regulations governing issuance of opinion letters on the status of ingredients under section 201(s) and 409 of the act in § 121.11 (21 CFR 121.11), procedures for affirmation of GRAS status and determination of food additive status in §§ 121.40 and 121.41 (21 CFR 121.40 and 121.41), and procedures for codifying and limiting or revoking prior sanctions in § 121.4000 (21 CFR 121.4000).

In reviewing the comments received on the notices and proposals published on July 26, 1973, and preparing the final orders on these proposals that appear elsewhere in this issue of the FEDERAL REGISTER, the Commissioner has concluded that it would be advisable to revise some of the existing regulations in 21 CFR Part 121 to clarify the criteria for GRAS status, the differences between GRAS status and food additive status, and the procedures being used to conduct the current review of food ingredients.

GRAS STATUS

Section 201(s) of the act provides that a food ingredient may be determined to be GRAS on the basis either of scientific procedures or, if the ingredient was used in food prior to January 1, 1958, through experience based on common use in food. Prior to the current review of the safety of GRAS and prior-sanctioned ingredients, the precise implications of this provision of the act, and its relation to the food additive provisions of the act, had not been clarified.

Under section 409 of the act, a food additive is required to be proved to be safe through adequate scientific evidence. The Commissioner believes that Congress intended the phrase "scientific procedures" as used in section 201(s) of the act to have the same dimensions as the full reports of investigations required to prove the safety of a food additive under section 409 of the act. Accordingly, the Commissioner proposes to define "scientific

procedures" to include those scientific studies appropriate to establish the safety of a substance. General recognition of safety through scientific procedures under section 201(s) would therefore require the same quantity and quality of scientific evidence as is required for proof of safety under section 409. This is consistent with the recent decisions of the Supreme Court in *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973) and *Weinberger v. Bentex Pharmaceuticals, Inc.*, 412 U.S. 645 (1973), where the Court held that the reach of scientific inquiry under the comparable provisions of sections 505(b) and 201(p) is "precisely the same".

The Commissioner also proposes to require that general recognition of safety must ordinarily be based upon published literature. This is consistent with the Supreme Court's statement in the *Bentex* decision that whether a particular drug is a "new drug" depends in part on the expert knowledge and experience of scientists based on controlled clinical experimentation and backed by "substantial support in scientific literature". Although the Supreme Court was there referring to new drugs rather than to food additives, and to effectiveness rather than to safety, the underlying legal issues are indistinguishable.

Unlike the definition of a "new drug" in section 201(p), however, under section 201(s) a food ingredient may become generally recognized as safe solely through common use in food if it was marketed prior to January 1, 1958. For such ingredients, scientific procedures are not required either to establish GRAS status or to obtain a food additive regulation to permit continued marketing. Accordingly, the Commissioner proposes to define "common use in food" to mean a substantial history of consumption of a substance by a significant number of consumers in the United States, and explicitly to recognize that, under the law, GRAS status based upon such a determination does not require or involve the same quantity or quality of scientific evidence that would be required for approval of a food additive regulation.

This is a particularly important concept under the law. The current review of GRAS and prior-sanctioned ingredients used in food has made it clear that, for a large number of food ingredients marketed prior to 1958, scientific studies of the types now required for approval of food additives have never been undertaken. This includes virtually all raw agricultural commodities and other substances of natural biological origin. A requirement that all of these foods be tested according to modern standards for new food additives would be a substantial misallocation of the country's testing resources and would represent a serious misordering of priorities. Where significant safety questions arise, immediate new testing can and will be required. Where no known hazard exists for pre-1958 ingredients, however, the law clearly contemplates that the full

battery of tests for a new food additive is not to be required.

For substances introduced into food after 1958, GRAS status may not be achieved through experience based on common use in food. For such substances, GRAS status may be determined, if at all, solely on the basis of scientific procedures, i.e., the same quantity and quality of scientific evidence as is necessary to obtain approval of a food additive at this time.

Section 201(s) of the act does provide; however, that such GRAS status may be achieved for post-1958 food ingredients on the basis of scientific procedures even prior to any significant history of marketing and use. Unlike the definition of "new drug" in section 201(p) of the act, section 201(s) does not require that a food ingredient be used "to a material extent or for a material time" before it may become GRAS.

On the other hand, general recognition of safety through scientific procedures does require that the scientific evidence on the basis of which this status is achieved has been published in the literature or otherwise widely disseminated throughout the scientific community knowledgeable about the safety of food ingredients, and that this evidence has indeed become common knowledge among such scientists. Accordingly, there will be at least some gap between the gathering of the scientific knowledge necessary to provide the toxicological underpinning for general recognition of safety and the dissemination to and assimilation by the scientific community of this material that is necessary for general recognition of safety to exist.

The Commissioner recognizes that it is not feasible at this time to prepare a list of all GRAS substances, and that such a list may well not be feasible for many years to come. GRAS status for raw agricultural commodities and other substances of natural biological origin that have been in common use prior to 1958 will ordinarily not require promulgation of a regulation in the FEDERAL REGISTER, unless a new type of processing is instituted. Instead, priority will be given to review of the status of food ingredients for which new processing methods have been introduced since 1958 or for which other significant alteration of composition has been made, synthetic food ingredients, substances intended for consumption for other than their nutrient properties, products extracted or otherwise obtained from GRAS substances, and other food ingredients for which safety questions have arisen. Once this lengthy list of substances is reviewed, it may then be feasible to return to matters of lower priority, and ultimately to develop a comprehensive GRAS list.

In the past, it has been too often assumed that a GRAS substance may be used in any food, at any level, for any purpose. As a result, the uses of some GRAS food ingredients have proliferated

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to the point where their GRAS status has been brought into serious question.

The Commissioner has concluded that there should be three types of regulations affirming the GRAS status of an ingredient. Where it is concluded after general evaluation of use of an ingredient that it is GRAS under conditions of use that presently exist or that are reasonably foreseeable, it is sufficient that the regulation affirming GRAS status state that it may be used under good manufacturing practices. This type of regulation will contain the conditions and levels of use that have been reported by the 1972 NAS/NRC survey on food manufacturers pursuant to current good manufacturing practices. These reported conditions of use (the function for which it is used, the food categories in which it is used, and the maximum levels at which it is used) are not intended as rigid limitations. Variations in use of a GRAS ingredient subject to this type of regulation will be permitted as long as the new conditions of use are not significantly different from those on the basis of which the GRAS status of the substance was affirmed.

For some GRAS ingredients, however, GRAS status is affirmed after general evaluation of their use only on the basis of existing use patterns, and not on the basis of possible increase in use. For these substances, the Commissioner proposes to establish rigid limitations in the regulations affirming the ingredient as GRAS. Any use of the ingredient under conditions other than those explicitly set out in the regulation (e.g., a use in a different category of food, or for a different functional purpose, or at a higher level) will automatically require a food additive regulation prior to such use. Thus, these limitations have the same effect as a limitation in a food additive regulation.

Where a general evaluation of use of an ingredient has not been made, specific uses of the ingredient may nevertheless be affirmed as GRAS. Petitions to affirm the GRAS status of substances under such circumstances are invited by § 121.40(c) (21 CFR 121.40(c)). Although a general evaluation of all uses of an ingredient is pertinent to its GRAS status, it is not feasible to make such an evaluation whenever a specific use is sought to be affirmed as GRAS. Such an evaluation would eventually be made in the course of development of a comprehensive GRAS list, however. The Commissioner proposes that specific uses be affirmed as GRAS, subject to reconsideration when general evaluation is undertaken. A regulation issued prior to general evaluation of use of an ingredient would not necessarily list all uses that are GRAS.

The Commissioner believes that the type of experience based on common use in food that will support a GRAS determination must involve use in the United States, and not solely in foreign countries. Reported use in foreign countries often cannot be verified, and in any event the experience based upon such use cannot be monitored or evaluated. Food

consumption patterns and differences between cultures make it impossible to assess whether a history of use abroad would be comparable to a history of use in the United States.

The determination that a food ingredient is GRAS is generally made on a product of specific composition, produced by one or more known manufacturing processes. This is particularly important where GRAS status is determined through experience based on common use in food, rather than through scientific procedures, because any change in a manufacturing process makes the relevance of the prior experience questionable. Accordingly, the Commissioner regards it as important that regulations affirming the GRAS status of an ingredient specify the manufacturing process used to obtain the ingredient that has been determined to be GRAS, and differentiate it from other possible versions of the ingredient that have not yet been determined to be GRAS. Other processes of manufacture may significantly alter the composition, and perhaps the toxicity, of the ingredient.

A change in manufacturing process may or may not require a food additive regulation, depending upon the information available about it. In any event, consideration must be given to the new process, to determine whether additional specifications or limitations are required to assure that the new version of the ingredient is not significantly different from the version that has been determined to be GRAS.

PRIOR SANCTIONS

The present review of GRAS and prior-sanctioned ingredients has required development of a means of ascertaining the existence or waiving the applicability of prior sanctions for use of such ingredients in food through approvals granted by the United States Department of Agriculture and the Food and Drug Administration prior to the effective date of the Food Additives Amendment of 1958, i.e., September 6, 1958. In the FEDERAL REGISTER of July 26, 1973 (38 FR 20041, 20048), the Commissioner proposed new regulations (21 CFR 121.104 and 121.105) incorporating a procedure for accomplishing this. Elsewhere in this issue of the FEDERAL REGISTER, the Commissioner is publishing final regulations incorporating this procedure without change. Any person who wishes to assert or at any time rely upon a prior sanction is required to submit proof of such prior sanction when a GRAS affirmation regulation is proposed. The failure to do so constitutes a waiver of any such prior sanction. The Commissioner has concluded that this procedure should be incorporated in other provisions of the regulations so that it will apply uniformly whenever regulations are adopted setting restrictions or limitations on ingredients where prior sanctions may possibly exist.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 402, 409, 701(a), 52 Stat. 1046-1047 as amended, 1055, 72

Stat. 1784-1788 as amended; 21 U.S.C. 321(s), 342, 348, 371(a)) and under authority delegated to him (21 CFR 2.120), the Commissioner proposes to amend Part 121:

1. In § 121.1 by revising paragraph (f), (h), (i) and (k), and by adding new paragraphs (l) and (m) as follows.

§ 121.1 Definitions and interpretations.

(f) "Common use in food" means a substantial history of consumption of a substance by a significant number of consumers in the United States.

(h) "Scientific procedures" include those human, animal, analytical, and other scientific studies, whether published or unpublished, appropriate to establish the safety of a substance.

(i) "Safe" or "safety" means that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful. It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of any substance. Safety may be determined by scientific procedures or by general recognition of safety. In determining safety, the following factors shall be considered:

(1) The probable consumption of the substance and of any substance formed in or on food because of its use.

(2) The cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet.

(3) Safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of food and food ingredients, are generally recognized as appropriate.

(4) The benefit contributed by the substance.

(k) "General recognition of safety" shall be determined in accordance with § 121.3.

(l) "Prior sanction" means an explicit approval granted with respect to use of a substance in food prior to September 6, 1958, by the United States Department of Agriculture or the Food and Drug Administration pursuant to the Federal Food, Drug, and Cosmetic Act, the Poultry Products Inspection Act, or the Meat Inspection Act.

(m) "Food" includes human food, substances migrating to food from food-contact articles, pet food, and animal feed.

2. By revising § 121.3 to read as follows:

§ 121.3 Classification of a food ingredient as generally recognized as safe (GRAS).

(a) General recognition of safety may be based upon either (1) scientific procedures or (2) in the case of a substance used in food prior to January 1, 1958, through experience based on common use in food. General recognition of safety

requires common knowledge about the substance throughout the scientific community knowledgeable about the safety of food ingredients.

(b) General recognition of safety based upon scientific procedures shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive regulation for the ingredient. General recognition of safety through scientific procedures shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data and information.

(c) General recognition of safety through experience based on common use in food prior to January 1, 1958, may be determined without the quantity or quality of scientific procedures required for approval of a food additive regulation. General recognition of safety through experience based on common use in food prior to January 1, 1958, shall ordinarily be based upon generally available data and information. An ingredient not in common use in food prior to January 1, 1958, may achieve general recognition of safety only through scientific procedures.

(d) The food ingredients listed as GRAS in § 121.101 or affirmed as GRAS in § 121.104 or § 121.105 do not include all substances that are generally recognized as safe for their intended use in food. Because of the large number of substances the intended use of which results or may reasonably be expected to result, directly or indirectly, in their becoming a component or otherwise affecting the characteristics of food, it is impracticable to list all such substances that are GRAS. A food ingredient of natural biological origin that has been widely consumed for its nutrient properties in the United States prior to January 1, 1958, without known detrimental effects, which is subject only to conventional processing as practiced prior to January 1, 1958, and for which no known safety hazard exists, will ordinarily be regarded as GRAS without specific inclusion in §§ 121.101, 121.104, or 121.105.

(e) Food ingredients were listed as GRAS in § 121.101 during 1958-1962 without a detailed scientific review of all available data and information relating to their safety. Beginning in 1969, the Food and Drug Administration has undertaken a systematic review of the status of all ingredients used in food on the determination that they are GRAS or subject to a prior sanction. All determinations of GRAS status or food additive status or prior sanction status pursuant to this review shall be handled pursuant to §§ 121.40, 121.41, and 121.4000. Affirmation of GRAS status shall be handled pursuant to §§ 121.104 or 121.105. The result of such review shall also be made known by an appropriate reference under the heading for the column "Limitations, restrictions, or explanations" in the tables in § 121.101.

(f) The status of the following food ingredients will be reviewed and affirmed as GRAS or determined to be a food ad-

ditive or subject to a prior sanction pursuant to §§ 121.40, 121.41, or 121.4000.

(1) Any substance of natural biological origin that has been widely consumed for its nutrient properties in the United States prior to January 1, 1958, without known detrimental effect, for which no health hazard is known, and which has been modified by processes first introduced into commercial use after January 1, 1958, which may reasonably be expected significantly to alter the composition of the substance.

(2) Any substance of natural biological origin that has been widely consumed for its nutrient properties in the United States prior to January 1, 1958, without known detrimental effect, for which no health hazard is known, that has had significant alteration of composition by breeding or selection after January 1, 1958, where the change may be reasonably expected to alter the nutritive value or the concentration of toxic constituents.

(3) Distillates, isolates, extracts, concentration of extracts, or reaction products of GRAS substances.

(4) Substances not of a natural biological origin, including those for which evidence is offered that they are identical to a GRAS counterpart of natural biological origin.

(5) Substances of natural biological origin intended for consumption for other than their nutrient properties.

(g) A food ingredient that is not GRAS or subject to a prior sanction requires a food additive regulation promulgated under section 409 of the act or a tolerance or action level promulgated under Part 122 of this chapter before it may be used in food as an added substance.

(h) Unless it is affirmed as GRAS for a specific use prior to general evaluation of use of the ingredient, a food ingredient that is listed as GRAS in § 121.101 or affirmed as GRAS in §§ 121.104 or 121.105 shall be regarded as GRAS only if, in addition to all the requirements in the applicable regulation, it also meets all of the following requirements:

(1) It complies with any applicable food grade specifications of the Food Chemicals Codex, 2d Ed. (1972).¹

(2) It performs an appropriate function in the food in which it is used.

(3) It is used at a level no higher than necessary to achieve its intended purpose in that food.

(4) If it is affirmed as GRAS in §§ 121.104 or 121.105 with no limitation other than good manufacturing practices, its conditions of use are not significantly different from those reported in the regulation as the basis on which the GRAS status of the substance was affirmed.

(5) If it is affirmed as GRAS in §§ 121.104 or 121.105 with specific limitation(s), it is used in food only within such limitation(s) (including the category of

food(s), the functional use(s) of the ingredient, and the level(s) of use). Any use of such an ingredient not in full compliance with each such established limitation shall require a food additive regulation.

(i) A food ingredient that is affirmed as GRAS in §§ 121.104 or 121.105 for a specific use(s), prior to general evaluation of use of the ingredient, shall be regarded as GRAS if, in addition to all the requirements in the applicable regulation, it meets the requirements of paragraph (h) (1), (2), and (3) of this section. In addition to the use(s) specified in the applicable regulation, other uses of such an ingredient may also be GRAS. Any affirmation of GRAS status for a specific use(s), prior to general evaluation of use of the ingredient, is subject to reconsideration upon such evaluation.

(j) New information may at any time require reconsideration of the GRAS status of a food ingredient. Any change in §§ 121.101, 121.104, or 121.105 shall be accomplished pursuant to § 121.41.

3. By adding a new § 121.14 to read as follows:

§ 121.14 Prior sanctions.

(a) A prior sanction shall exist only for a specific use(s) of a substance in food, i.e., the level(s), condition(s), product(s), etc., for which there was explicit approval by the Food and Drug Administration or the United States Department of Agriculture prior to September 6, 1958.

(b) The existence of a prior sanction exempts the sanctioned use(s) from the food additive provisions of the act but not from the other adulteration or the misbranding provisions of the act.

(c) All known prior sanctions shall be the subject of a regulation published in Subpart E of this part. Any such regulation is subject to amendment to impose whatever limitation(s) or condition(s) may be necessary for the safe use of the ingredient, or revocation to prohibit use of the ingredient, in order to prevent the adulteration of food in violation of section 402 of the act.

(d) In proposing regulations affirming the GRAS status of substances added directly to human food in § 121.104 or substances in food-contact surfaces in § 121.105, or in establishing a food additive regulation for substances added directly to human food in Subpart D of this part or food additives in food-contact surfaces in Subpart F of this part, the Commissioner shall, if he is aware of any prior sanction for use of the ingredient under conditions different from those proposed in the regulation, concurrently propose a separate regulation covering such use of the ingredient under Subpart E of this part. If the Commissioner is unaware of any such applicable prior sanction, the proposed regulation will so state and will require any person who intends to assert or rely on such sanction to submit proof of its existence. Any food additive or GRAS regulation promulgated pursuant to this part constitutes a determination that excluded uses would

¹ Copies may be obtained from: National Academy of Sciences, 2101 Constitution Ave. NW., Washington, D.C. 20087.

result in adulteration of the food in violation of section 402 of the act, and the failure of any person to come forward with proof of such an applicable prior sanction in response to a proposal will constitute a waiver of the right to assert or rely on such sanction at any later time. The notice will also constitute a proposal to establish a regulation under Subpart E, incorporating the same provisions, in the event that such a regulation is determined to be appropriate as a result of submission of proof of such an applicable prior sanction in response to the proposal.

4. By amending § 121.40 to add the following new paragraph (c) (6) to read as follows:

§ 121.40 Affirmation of generally recognized as safe (GRAS) status.

(c) * * *

(6) The notice of filing in the FEDERAL REGISTER will request submission of proof of any applicable prior sanction for use of the ingredient under conditions different from those proposed to be determined to be GRAS. The failure of any person to come forward with proof of such an applicable prior sanction in response to the notice of filing will constitute a waiver of the right to assert or rely on such sanction at any later time. The notice of filing will also constitute a proposal to establish a regulation under Subpart E, incorporating the same provisions, in the event that such a regulation is determined to be appropriate as a result of submission of proof of such an applicable prior sanction in response to the notice of filing.

5. By amending § 121.41 to add a new paragraph (d) to read as follows:

§ 121.41 Determination of food additive status.

(d) If the Commissioner of Food and Drugs is aware of any prior sanction for use of the substance, he will concurrently propose a separate regulation covering such use of the ingredient under Subpart E of this part. If the Commissioner is unaware of any such applicable prior sanction, the proposed regulation will so state and will require any person who intends to assert or rely on such sanction to submit proof of its existence. Any regulation promulgated pursuant to this section constitutes a determination that excluded uses would result in adulteration of the food in violation of section 402 of the act, and the failure of any person to come forward with proof of such an applicable prior sanction in response to the proposal will constitute a waiver of the right to assert or rely on such sanction at any later time. The notice will also constitute a proposal to establish a regulation under Subpart E, incorporating the same provisions, in the event that such a regulation is determined to be appropriate as a result of submission of proof of such an applicable sanction in response to the proposal.

6. By amending § 121.104 to add a new sentence to paragraph (a) and by adding

new subparagraphs (1), (2), and (3) to paragraph (b) to read as follows:

§ 121.104 Substances added directly to human food affirmed as generally recognized as safe (GRAS).

(a) * * * The regulations in this section shall sufficiently describe each ingredient to identify the characteristics of the ingredient that has been affirmed as GRAS and to differentiate it from other possible versions of the ingredient that have not been affirmed as GRAS.

(b) * * *

(1) If the ingredient is affirmed as GRAS with no limitation other than good manufacturing practices, it shall be regarded as GRAS as long as its conditions of use are not significantly different from those reported in the regulation as the basis on which the GRAS status of the substance was affirmed.

(2) If the ingredient is affirmed as GRAS with specific limitation(s), it shall be used in food only within such limitation(s) (including the category of food(s), the functional use(s) of the ingredient, and the level(s) of use). Any use of such an ingredient not in full compliance with each such established limitation shall require a food additive regulation.

(3) If the ingredient is affirmed as GRAS for a specific use, prior to general evaluation of use of the ingredient, other uses may also be GRAS.

7. By amending § 121.105 to add a new sentence to paragraph (a) and by adding new subparagraphs (1) and (2) to paragraph (b) to read as follows:

§ 121.105 Substances in food contact surfaces affirmed as generally recognized as safe (GRAS).

(a) * * * The regulations in this section shall sufficiently describe each ingredient to identify the characteristics of the ingredient that has been affirmed as GRAS and to differentiate it from other possible versions of the ingredient that have not been affirmed as GRAS.

(b) * * *

(1) If the ingredient is affirmed as GRAS with no limitation other than good manufacturing practices, it shall be regarded as GRAS as long as its conditions of use are not significantly different from those reported in the regulation as the basis on which the GRAS status of the substance was affirmed.

(2) If the ingredient is affirmed as GRAS with specific limitation(s), it shall be used in food-contact surfaces only within such limitation(s) (including the category of food-contact surface(s), the functional use(s) of the ingredient, and the level(s) of use). Any use of such an ingredient not in full compliance with each such established limitation shall require a food additive regulation.

(3) If the ingredient is affirmed as GRAS for a specific use, prior to general evaluation of use of the ingredient, other uses may also be GRAS.

Interested persons may, on or before December 23, 1974, file with the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852, written comments (preferably in quintuplicate) regarding this proposal. Comments may be accompanied by a memorandum or brief in support thereof. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: September 9, 1974.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.74-21203 Filed 9-20-74; 8:45 am]

[21 CFR Part 121]

BENZOIC ACID AND SODIUM BENZOATE
Proposed Affirmation of GRAS Status as Direct Human-Food Ingredients

The Food and Drug Administration is conducting a comprehensive study of direct human food ingredients classified as generally recognized as safe (GRAS) or subject to a prior sanction. The Commissioner of Food and Drugs has issued several notices and proposed regulations, published in the FEDERAL REGISTER of July 26, 1973 (38 FR 20035-20057), implementing this review. Elsewhere in this issue of the FEDERAL REGISTER, the Commissioner is issuing the final regulations resulting from those proposals. Pursuant to this review, the safety of benzoic acid and sodium benzoate has been evaluated. In accordance with the provisions of § 121.40, the Commissioner proposes to affirm the GRAS status of these two ingredients.

Benzoic acid (benzencarboxylic acid) and its sodium salt, sodium benzoate (benzoate of soda) were listed in § 121.101(d)(2) as GRAS for use in food as chemical preservatives at a maximum of 0.1 percent, published in the FEDERAL REGISTER of November 20, 1959 (24 FR 9369). Subsequently, sodium benzoate was listed in § 121.2001 as prior-sanctioned for use in food as an antimicrobial in the manufacture of food-packaging materials in the FEDERAL REGISTER of February 2, 1960 (25 FR 866).

Benzoic acid and sodium benzoate have been the subject of a search of the scientific literature from 1920 to the present. The parameters used in the search were chosen to discover any articles that considered (1) chemical toxicity, (2) occupational hazards, (3) metabolism, (4) reaction products, (5) degradation products, (6) any reported carcinogenicity, teratogenicity or mutagenicity, (7) dose response, (8) reproductive effects, (9) histology, (10) embryology, (11) behavioral effects, (12) detection, and (13) processing. A total of 1527 abstracts on benzoates and benzoic acid was reviewed and 42 particularly pertinent reports from the literature survey have been summarized in a Scientific Literature Review.

A representative cross-section of food manufacturers was surveyed to determine the specific foods in which benzoic acid and sodium benzoate were used and

000056

§ 182.6219 Calcium phytate.

(a) *Product.* Calcium phytate.
 (b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.6285 Dipotassium phosphate.

(a) *Product.* Dipotassium phosphate.
 (b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.6290 Disodium phosphate.

(a) *Product.* Disodium phosphate.
 (b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.6386 Isopropyl citrate.

(a) *Product.* Isopropyl citrate.
 (b) *Tolerance.* This substance is generally recognized as safe for use at a level not exceeding 0.02 percent in accordance with good manufacturing practice.

§ 182.6511 Monoisopropyl citrate.

(a) *Product.* Monoisopropyl citrate.
 (b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.6625 Potassium citrate.

(a) *Product.* Potassium citrate.
 (b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.6751 Sodium citrate.

(a) *Product.* Sodium citrate.
 (b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.6754 Sodium diacetate.

(a) *Product.* Sodium diacetate.
 (b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.6757 Sodium gluconate.

(a) *Product.* Sodium gluconate.
 (b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.6760 Sodium hexametaphosphate.

(a) *Product.* Sodium hexametaphosphate.
 (b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.6769 Sodium metaphosphate.

(a) *Product.* Sodium metaphosphate.
 (b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.6778 Sodium phosphate.

(a) *Product.* Sodium phosphate (mono-, di-, and tribasic).
 (b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.6787 Sodium pyrophosphate.

(a) *Product.* Sodium pyrophosphate.
 (b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.6789 Tetra sodium pyrophosphate.

(a) *Product.* Tetra sodium pyrophosphate.
 (b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.6801 Sodium tartrate.

(a) *Product.* Sodium tartrate.
 (b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.6804 Sodium potassium tartrate.

(a) *Product.* Sodium potassium tartrate.
 (b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.6807 Sodium thiosulfate.

(a) *Product.* Sodium thiosulfate.
 (b) *Tolerance.* 0.1 percent.
 (c) *Limitations, restrictions, or explanation.* This substance is generally recognized as safe when used in salt in accordance with good manufacturing practice.

§ 182.6810 Sodium tripolyphosphate.

(a) *Product.* Sodium tripolyphosphate.
 (b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.6851 Stearyl citrate.

(a) *Product.* Stearyl citrate.
 (b) *Tolerance.* This substance is generally recognized as safe for use at a level not exceeding 0.15 percent in accordance with good manufacturing practice.

Subpart H—Stabilizers

§ 182.7115 Agar-agar.

(a) *Product.* Agar-agar.
 (b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.7133 Ammonium alginate.

(a) *Product.* Ammonium alginate.
 (b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.7187 Calcium alginate.

(a) *Product.* Calcium alginate.

(b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.7255 Chondrus extract.

(a) *Product.* Chondrus extract (carrageenin).
 (b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.7610 Potassium alginate.

(a) *Product.* Potassium alginate.
 (b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.7724 Sodium alginate.

(a) *Product.* Sodium alginate.
 (b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

PART 184—DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE

Subpart A—General Provisions

Sec. 184.1 Substances added directly to human food affirmed as generally recognized as safe (GRAS).

Subpart B—Listing of Specific Substances Affirmed as GRAS

- 184.1021 Benzoic acid.
- 184.1271 L-Cysteine.
- 184.1272 L-Cysteine monohydrochloride.
- 184.1282 Dill and its derivatives.
- 184.1298 Ethyl alcohol.
- 184.1317 Garlic and its derivatives.
- 184.1330 Acacia (gum arabic).
- 184.1338 Gum ghatti.
- 184.1339 Guar gum.
- 184.1343 Locust (carob) bean gum.
- 184.1349 Karaya gum (sterculia gum).
- 184.1351 Gum tragacanth.
- 184.1490 Methylparaben.
- 184.1600 Propyl gallate.
- 184.1670 Propylparaben.
- 184.1699 Oil of rue.
- 184.1733 Sodium benzoate.
- 184.1835 Sorbitol.
- 184.1983 Bakers yeast extract.

AUTHORITY: Secs. 409, 701, 82 Stat. 1055-1056 as amended; 72 Stat. 1735-1738 as amended (21 U.S.C. 348, 371), unless otherwise noted.

Subpart A—General Provisions

§ 184.1 Substances added directly to human food affirmed as generally recognized as safe (GRAS).

(a) The direct human food ingredients listed in this section have been reviewed by the Food and Drug Administration and determined to be generally recognized as safe (GRAS) for the purposes and under the conditions prescribed. The regulations in this section shall sufficiently describe each ingredient to identify the characteristics of the ingredient that has been affirmed as GRAS and to differentiate it from other possible versions of the ingredient that have not been affirmed as GRAS. Ingredients affirmed as GRAS in this

42
77

Reference List for Industry Submission, GRN 000058

Page Numbers	Publication
000017-000038	Life Sciences Research Office, Federation of American Societies for Experimental Biology. 1973. Evaluation of the Health Aspects of Gum Arabic as a Food Ingredient.
000039-000044	Joint FAO/WHO Expert Committee on Food Additives. Toxicological Evaluation Of Some Food Additives Including Anticaking Agents, Antimicrobials, Antioxidants, Emulsifiers and Thickening Agents, 1974, Series Number 5, World Health Organization Geneva
000045 - 000048	Joint FAO/WHO Expert Committee on Food Additives. Toxicological Evaluation Of Some Food Additives Including Anticaking Agents, Antimicrobials, Antioxidants, Emulsifiers and Thickening Agents, 1974, Series Number 53A, Food And Agriculture organization of the United Nations Rome