

PROPOSED RULES

lysts, flocculents, and filter aids, etc.): substances used as manufacturing aids to enhance the appeal or utility of a food or food component.

(23) "Propellants, aerating agents, and gasses": chemically inert gasses used to supply force to expel a product or used to reduce the amount of oxygen in contact with the food in packaging processes.

(24) "Sequestrants": substances which combine with polyvalent metal ions to form a soluble metal complex, to improve the quality and stability of products.

(25) "Solvents and vehicles": substances used to extract or dissolve another substance.

(26) "Stabilizers and thickeners" (including suspending and bodying agents, setting agents, jelling agents, and bulking agents, etc.): substances used to produce viscous solutions or dispersions, to impart body, improve consistency, or stabilize emulsification.

(27) "Surface-active agents" (other than emulsifiers, but including solubilizing agents, dispersants, detergents, wetting agents, rehydration enhancers, whipping agents, foaming agents, and defoaming agents, etc.): substances used to modify surface properties of food components for a variety of effects.

(28) "Surface-finishing agents" (including glazes, polishes, waxes, and protective coatings): substances used to increase palatability, preserve gloss, and inhibit discoloration of foods.

(29) "Sweeteners": substances used to sweeten the taste of food.

(30) "Synergists": substances used to act or react with another food ingredient to produce a total effect different or greater than the sum of the individual effects.

(31) "Texturizers": substances which affect the appearance or feel of the composition of a food.

Interested persons may, on or before October 24, 1973, file with the Hearing Clerk, Food and Drug Administration, Room 6-88, 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: July 19, 1973.

A. M. SCHMIDT,
Commissioner of Food and Drugs.
[FR Doc. 73-15217 Filed 7-25-73; 8:45 am]

[21 CFR Part 121]

MANNITOL AND SORBITOL

Affirmation of GRAS Status of 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. Pursuant to this review, the safety of mannitol and sorbitol has been evaluated. In accordance with the provisions of § 121.40, the Commissioner of Food and Drugs pro-

poses to affirm the GRAS status of these two ingredients.

Mannitol (1,2,3,4,5,6-hexanehexol) and its stereoisomer sorbitol are both solid hexahydric alcohols prepared commercially by catalytic reduction of glucose. Both occur naturally in small amounts in a variety of foods. Mannitol is found in olives, beets, celery and in the exudate of certain trees. Sorbitol is a normal constituent of such fruits as cherries, plums, pears, apples, and many berries.

Mannitol and sorbitol were listed in § 121.101(d) (2) as GRAS for use in special dietary foods at a maximum of 5 percent and 7 percent respectively in the FEDERAL REGISTER of January 31, 1961 (26 FR 938). Subsequently, food additive regulations were published for mannitol under § 121.1115 in the FEDERAL REGISTER of August 9, 1961 (26 FR 1540) and for sorbitol under § 121.1053 in the FEDERAL REGISTER of February 19, 1963 (26 FR 7127) to provide for other uses of these substances, with levels for use being restricted only to the amount reasonably required to accomplish the intended effect.

Mannitol and Sorbitol have been the subject of a search of the published 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) reported carcinogenicity, teratogenicity, or mutagenicity, (7) dose response, (8) reproductive effects, (9) histology, (10) embryology, (11) behavioral effects, (12) detection methodology and (13) processing. A total of 968 abstracts on mannitol were reviewed and 11 particularly pertinent reports from the literature survey have been summarized in a Scientific Literature Review. A total of 870 abstracts on sorbitol were reviewed and 26 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 these substances were 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 mannitol and sorbitol. The total mannitol used in food in 1970 is reported to be about 90 times that used in 1960. The total sorbitol used in food in 1970 is reported to be about seven times that used in food in 1960.

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

Mannitol is absorbed from the gastrointestinal tract of animals and man, and does not accumulate in the organism; it is partially metabolized and partly excreted in the urine. There is evidence that the intestinal flora may convert mannitol to more readily utilized substance, and this transformation may influence the reported amount of mannitol absorbed and metabolized by the liver. A

wide variety of microorganisms and fungi convert mannitol to sugars and other carbohydrate fragments.

The absorption of mannitol in a 50 cm segment of the proximal small intestine, in children varying in age from 8 months to 4 years, has been reported. The mannitol was perfused in an isotonic solution in concentrations varying from 50 to 150 millimoles per liter. From 9 to 18 percent of the mannitol was found to be absorbed.

A more extensive study in 16 human adult volunteers, ranging in age from 20 to 66, revealed that, in the oral dosage range of 40 to 100 g, 55 percent of the ingested mannitol was absorbed. Of the absorbed mannitol, about a third was excreted intact in the urine and the remainder was oxidized to carbon dioxide. Excretion was virtually complete by four days, with about 91 percent excreted within the first day.

In experiments where 25 g of mannitol were fed to normal men, little evidence was found that the substance was utilized, as measured by blood sugar levels or respiratory quotients. The threshold laxative dose was found to be between 10 and 20 g of mannitol as compared with 50 g of sorbitol.

There are no reported long-term animal feeding studies (extending for more than half of the life span of the species) on mannitol. Relevant short-term animal studies and studies on man are summarized below.

The oral LD₅₀ for the mouse is reported to be 22 g per kg, and for the rat to be 17.3 g per kg. The minimum lethal dose for the rat is reported to be greater than 13 g per kg.

In rats and monkeys fed mannitol (5 percent of the rat diet, and 3 g daily to monkeys) no significant chronic toxicity was observed over a period of 3 months. A study on one man, fed 10 g daily for a month, revealed no evidence of toxicity; but the same authors have shown that the ingestion of 10 to 20 g of crystalline mannitol as part of the diet results in a laxative effect. The latter observation has been confirmed.

Preliminary teratologic tests in mice, rats, and hamsters have been negative. Oral doses up to 1.8 g per kg of body weight of mannitol to pregnant mice and rats for 10 consecutive days, or up to 1.2 g per kg of body weight to pregnant hamsters for 5 consecutive days, produced no clearly discernible effects or nidation or on maternal or fetal survival. The frequency of abnormalities in either soft or skeletal tissues of the test animals was comparable to that occurring spontaneously in the sham-treated controls.

The Select Committee is unaware of any reports on mannitol indicating evidence of its carcinogenicity, mutagenicity, or effects on reproduction.

When injected intravenously, mannitol is filtered by the glomeruli of the kidneys and not appreciably reabsorbed by the tubules. For this reason, mannitol has been employed extensively as a substance to measure glomerular filtration rate in man. It has also been used medically as an intravenous diuretic, to lower intracranial pressure, and to decrease intraocular pressure in glaucoma. This wide usage of mannitol has not resulted in untoward toxic effects. However, a single allergic reaction to mannitol was observed when the substance was administered intravenously for the treatment of glaucoma. In the experience of these investigators, over 1500 patients had received similar medication without a serious allergic reaction. It appears from this report that allergic reactions to mannitol are possible, but that it does not constitute a dietary hazard for this reason.

The Joint FAO/WHO Expert Committee on Food Additives classified mannitol, in amounts of 50-150 mg per kg of body weight daily, as "conditionally acceptable". This term means that the substance may be employed within the specified limits with an

PROPOSED RULES

adequate margin of safety if it has been reviewed by experts for a particular use.

Orally administered sorbitol is absorbed and metabolized rapidly by man through normal glycolytic pathways, ultimately to carbon dioxide and water. After a 35 g dose (equivalent to 583 mg per kg) in normal and in diabetic adults, for example, less than 3 percent of the sorbitol was excreted in the urine in any case and the concentration of sorbitol in the blood was found to be immeasurably small. No evidence of toxicity was reported.

The oral LD₅₀ of sorbitol in male and female mice is reported to be 23,200 and 25,700 mg per kg respectively; in male and female rats, 17,500 and 15,900 mg per kg respectively. The oral LD₅₀ for the male rat is separately reported as 26,000 mg per kg.

The following short term studies of the oral administration of sorbitol are relevant:

In 40 g male rats, fed 5 percent sorbitol in a balanced diet, no toxic effects were observed during the three months of feeding. Feed consumption is not reported, but estimates based on other data presented indicate that sorbitol was being fed at a level of approximately 5 g per kg per day.

Rhesus monkeys fed sorbitol at a level of 8 g per kg per day for 3 months remained unaffected.

Man, consuming 10 g of sorbitol each day (equivalent to 167 mg per kg) for one month remained unaffected.

Normal children, 5-6 years old and normal infants, 20-35 months old, fed 9.3 g of sorbitol (equivalent to 500 or more mg per kg) remained unaffected except for the appearance of diarrheal stools in the younger group.

The laxative threshold for sorbitol, established in 12 normal adults, has been reported to be 50 g (equivalent to 833 mg per kg). It is also reported, in a study involving 86 volunteers, that a dosage level of 25 g per day in two doses does not cause laxation.

The following long-term studies of the oral administration of sorbitol are relevant:

Rats fed 5 percent sorbitol (equivalent to 8 g per kg per day) through three generations showed no deleterious effects on growth rate or liver glycogen storage capacity. There were no gross or histological abnormalities in kidney, liver, spleen, pancreas, or duodenum attributable to sorbitol. A subsequent report has indicated that weanling rats, given sorbitol at levels of 10 to 15 percent in the diet for 17 months and observed over 4 successive generations, showed no evidence of deleterious effects on weight gain, reproduction, lactation, or histological appearance of the main organs.

Rats fed 16 percent sorbitol for 19 months showed a tendency to become hypercalcemic after one year, with the appearance in some animals of bladder concretions and a generalized thickening of the skeleton. No feed consumption or animal weight figures were reported, but sorbitol level was estimated to be of the order of 16 g per kg.

No oral studies of the carcinogenic activity of sorbitol have been reported. However, studies in rats revealed that injected sorbitol, in the form of an iron-sorbitol citric acid product (Jectofer), produced no injection site tumors.

Sorbitol, at dose levels of 5 g per kg did not produce any measurable mutagenic response in the host-mediated assay in mice, in the metaphase chromosomes of rat bone marrow, or in the dominant lethal test in the rat. A slight increase was noted in the mitotic recombination frequency for *Saccharomyces cerevisiae* in the host-mediated assay, and a moderate, dose-related adverse effect was exhibited by human embryonic lung cells scored at anaphase.

Sorbitol elicited no teratogenic response in pregnant mice or rats fed a daily dose of

1600 mg per kg for 10 days, or in hamsters fed 1200 mg per kg per day for 5 days.

The Joint Food and Agriculture Organization/World Health Organization Committee on Food Additives indicates the acceptable daily intake of sorbitol for man as follows: "Conditional acceptance (as a food additive or as a food) not limited".

All of the available safety information has been carefully evaluated by qualified scientists of the Select Committee on GRAS Substances selected by the Life Sciences Office of the Federation of American Societies for Experimental Biology (FASEB). It is the opinion of the Select Committee that there is no evidence in the available information on sorbitol and mannitol that demonstrates a hazard to the public when they are used at current levels or at levels that may reasonably be expected in the future. Based upon his own evaluation of this information the Commissioner concurs with this conclusion.

Copies of the Scientific Literature Reviews on mannitol and sorbitol and the reports of the FASEB Committee are

available for review at the office of the Hearing Clerk, Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20852, and may be purchased from the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA 22151.

Therefore, pursuant to provisions of the Federal Food, Drug and Cosmetic Act (secs. 201(a), 409(d), 701(a); 52 Stat. 1055, 72 Stat. 1784, 1787; 21 U.S.C. 321(a), 348(d), 371(a)) and under authority delegated to him (21 CFR 2.120), the Commissioner proposes that Part 121 be amended as follows:

1. In the table in § 121.101(d) by amending the listing for "Mannitol" and "Sorbitol" in the "Tolerance" and in the "Limitations, restrictions or explanations" columns in subparagraph (d) (5) to read as follows:

§ 121.101 Substances that are generally recognized as safe.

(d) * * *

Product	Tolerance	Limitations, restrictions or explanations
...
(5) NUTRIENTS AND/OR DIETARY SUPPLEMENTS ¹
Mannitol.....	Affirmed as GRAS § 121.104(g)(3).
Sorbitol.....	Affirmed as GRAS § 121.104(g)(4).

§§ 121.1053 and 121.1115 [Revoked].

2. By revoking § 121.1053 and § 121.1115

3. By amending proposed new § 121.104 to add the following two new subparagraphs to paragraph (g).

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

(g) * * *

(3) *Mannitol*. (i) Mannitol is the chemical 1,2,3,4,5,6,-hexanehexol (C₆H₁₄O₆), produced by the electrolytic reduction of glucose, differing principally from sorbitol by having a different optical rotation.

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

(iii) The ingredient is used as a sweetener, formulating aid, stabilizer and thickener, and surface-finishing agent.

(iv) The ingredient is used in food at levels not to exceed good manufacturing practices. The 1972 NAS-NRC Survey indicates current good manufacturing practice in the use of mannitol results in a maximum of 33 percent in hard candy (§ 121.1(d) (25)), 25 percent in chewing gum § 121.1(d) (6), 40 percent in soft candy (§ 121.1(d) (38)), 8 percent in confections and frostings (§ 121.1(d) (9)), and at less than 2.5 percent in all other foods.

(v) The label and labeling of food whose reasonably foreseeable consumption may result in a daily ingestion of 20

grams of mannitol shall bear the statement: "Excess consumption may have a laxative effect."

(4) *Sorbitol*. (i) Sorbitol is the chemical 1,2,3,4,5,6,-hexanehexol (C₆H₁₄O₆), produced by the electrolytic reduction of glucose, differing principally from mannitol by having a different optical rotation.

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

(iii) The ingredient is used as a sweetener, formulating aid, emulsifier, humectant, stabilizer and thickener, texturizer, lubricant, and anticaking agent.

(iv) The ingredient is used in foods at levels not to exceed good manufacturing practices. The 1972 NAS-NRC Survey indicates current good manufacturing practice in the use of sorbitol results in a maximum of 97 percent in hard candy (§ 121.1(d) (25)), 62 percent in chewing gum (§ 121.1(d) (6)), 98 percent in soft candy (§ 121.1(d) (38)), 17 percent in frozen dairy desserts and mixes (§ 121.1(d) (20)), 30 percent in baked goods and baking mixes (§ 121.1(d) (1)), and 8 percent or less in all other foods.

(v) The label and labeling of food whose reasonably foreseeable consumption may result in a daily ingestion of 50 grams of sorbitol shall bear the statement: "Excess consumption may have a laxative effect."

¹ Copies may be obtained from: National Academy of Sciences, 2101 Constitution Avenue, N.W. Washington, D.C. 20037.

PROPOSED RULES

The Commissioner hereby gives notice that he is unaware of any prior-sanction for the use of this ingredient in food under the conditions different from those proposed above. Any person who intends to assert or rely on such a sanction shall submit proof of its existence in response to this proposal. The regulations 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 such 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 October 24, 1973, file with the Hearing Clerk, Food and Drug Administration, Rm. 6-88, 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: July 19, 1973.

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

[FR Doc. 73-15214 Filed 7-25-73; 8:45 am]

[21 CFR Part 121]

METHYL PARABEN AND PROPYL PARABEN

Affirmation of GRAS Status of 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. Pursuant to this review, the safety of methyl paraben and propyl paraben has been evaluated. In accordance with the provisions of § 121.40, the Commissioner of Food and Drugs proposes to affirm the GRAS status of these two ingredients. The Commissioner also proposes to establish a new § 121.104, under which all direct human food ingredients affirmed as GRAS will be listed.

As the review of GRAS and prior-sanctioned direct human food ingredients progresses, these ingredients will be proposed for inclusion in new § 121.104 *Substances added directly to human food affirmed as generally recognized as safe (GRAS)*, proposed new § 121.106 *Substances prohibited from use in food*, Subpart D as direct human food additives, Subpart E as prior sanctions, or Subpart H as interim food additives. Because § 121.101 is not limited to direct human food ingredients, and has been regarded also as the basis of GRAS determinations for indirect food ingredient use (in or

on food contact surfaces), and for use in pet food and animal feed, the Commissioner has concluded that when an ingredient listed in § 121.101 is affirmed for direct human food use, it will be retained in § 121.101 with the explanation that it has been affirmed as GRAS and cross-referenced to the applicable paragraph in new § 121.104. This procedure is proposed with respect to methyl paraben and propyl paraben.

Many of the substances published as GRAS in § 121.101, or used on a determination that they are GRAS without publication in § 121.101 were approved by the United States Department of Agriculture for use in meat or poultry, or were approved by the Food and Drug Administration for use in various foods pursuant to correspondence, food standards, regulation, informal announcements, or in other ways, prior to 1958. Thus, many of these ingredients are subject to specific prior sanctions in addition to GRAS status. No comprehensive list of such prior sanctions exists. To the extent that one of these substances is affirmed as GRAS for all prior-sanctioned uses, the fact that it may also be subject to a prior sanction is largely of historical interest and has no regulatory significance. To the extent that one of these substances is not affirmed as GRAS for all prior-sanctioned uses, any restrictions or limitations imposed upon its use could in any event also be imposed on the prior-sanctioned uses under the adulteration provisions of the act as provided in § 121.2000, published in the FEDERAL REGISTER of May 15, 1973 (38 FR 12738).

Accordingly, the Commissioner has concluded that regulations based upon the review of GRAS and prior-sanctioned direct human food ingredients will initially be proposed on the assumption that no prior sanction exists. Because prior-sanctioned status constitutes an exemption from section 409 of the Act, it should be construed narrowly, and the burden of coming forward with evidence of the sanction properly rests upon the person who asserts it. In the event that any person responds to a proposed regulation with proof of a valid prior-sanction, a final regulation will be issued under Subpart E "Substances for which prior sanctions have been granted," as well as under any other applicable sections of the regulations. In this way, all possible uses of the ingredient will be fully covered. Any regulation promulgated pursuant to this review 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 to submit proof of an applicable prior sanction in response to any proposed regulation will also constitute a waiver of the right to assert such sanction at any later point in time. Any proposed regulation will also be construed as a proposal under Subpart E in the event that a prior sanction is asserted in comments submitted on it. This procedure is necessary because of the unavailability of any comprehensive list of prior sanctions.

Methyl paraben (methyl-*p*-hydroxybenzoate) and propyl paraben (propyl-*p*-hydroxybenzoate) were listed in § 121.101(d)(2) as GRAS for use as preservatives in food at a maximum of 0.1 percent, following a proposal published in the FEDERAL REGISTER of January 31, 1961 (26 FR 938).

Methyl paraben and propyl paraben have been the subject of a search of the published 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) occupation 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 methodology, and (13) processing. A total of 325 abstracts on the parabens were reviewed and 33 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 these substances were 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 methyl paraben and propyl paraben. The total methyl paraben used in food in 1970 is reported to be about 16 times that used in 1960. The total propyl paraben used in food in 1970 is reported to be about 30 times that used in 1960.

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

"Studies in rats, rabbits, dogs, cats, and man show that methyl and propyl paraben are absorbed from the gastrointestinal tract and metabolized. Neither is accumulated in the body. The major metabolites, in decreasing concentrations in the urine, are *p*-hydroxybenzoic acid and the glycine, glucuronic acid, and sulfuric acid conjugates of *p*-hydroxybenzoic acid. Most, but probably not all of the ingested parabens, is metabolized to the foregoing substances through normal pathways in the liver and kidneys. The following work is particularly significant.

In rabbits, 86 percent of a single 400 mg or 800 mg dose of methyl paraben was excreted within 24 hours as *p*-hydroxybenzoic acid (39 percent), hippuric acid (15 percent), the glucuronic ester and ether (22 percent), and sulfuric acid conjugates (10 percent). In rabbits, 70 percent of a single 400 mg dose of propyl paraben was excreted as the same metabolites within 9 hours, 85 percent within 24 hours, and 88 percent within 48 hours.

In dogs, 66 percent of a 1.0 g per kg oral dose of methyl paraben was excreted within 24 hours (89 percent within 48 hours) as *p*-hydroxybenzoic acid and glucuronic acid conjugates. No accumulation of either methyl or propyl paraben was observed when 1.0 g per kg was administered daily for one year; the rate of excretion of the administered dose increased to 96 percent each 24 hours during that period.

In a fasted man, 50 percent of a dose of 70 mg per kg of methyl paraben was excreted as *p*-hydroxybenzoic acid and conjugates with-