

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-

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in 12 hours. In another human subject, 55 percent of a daily 2.0 g dose of propyl paraben was excreted as sulfuric acid conjugates. Inasmuch as the authors were unable to account for all of the administered paraben as the foregoing excretion products, it was concluded that some cleavage of the benzene ring may occur metabolically.

Relevant short-term animals studies (extending for less than half of the life span of the species) and studies on man are summarized below. There is a dearth of closely controlled experimental data.

The oral LD₅₀ of both methyl paraben and propyl paraben for the mouse is reported to be greater than 8,000 mg per kg. The oral LD₅₀ of methyl paraben is reported to be 3,000 mg per kg for the rabbit and 2,000 mg per kg for the dog; that for propyl paraben is 8,000 mg per kg for the rabbit and 3,000 to 4,000 mg per kg for the dog.

Dogs fed as much as 1,000 mg per kg per day of methyl or propyl paraben six days weekly for one year exhibited no toxic symptoms, and blood samples were normal. One female that had been receiving 500 mg per kg per day of methyl paraben for one year was mated and delivered a litter of healthy pups. In other experiments, two dogs were unaffected by oral methyl or propyl paraben levels of 500 mg per kg per day, but evidence of toxicity appeared at 2,000 mg per kg per day of methyl paraben and at 4,000 mg per kg per day of propyl paraben.

Growth of young rats, thought at first to be retarded by oral doses of 250 and 500 mg per kg per day of methyl paraben (period of feeding not reported), was found to be unaffected when these experiments were extensively repeated.

Rabbits fed methyl or propyl paraben at 500 mg per kg per day for 6 days showed no ill effects. With both compounds, first distinct toxic effects were reported to appear when fed at 3,000 mg per kg per day.

A human volunteer, ingesting 2,000 mg of methyl paraben daily for one month was unaffected. Similarly, a human volunteer ingesting 2,000 mg of propyl paraben daily for one month exhibited no visible toxic effects. One experimenter reported that he ingested 2,000 mg of methyl paraben daily for an unstated period and "was able to ascertain an innocuousness even with prolonged use and in doses considerably greater than the minimum necessary in its practical application".

Methyl paraben elicited no teratogenic response in pregnant mice or rats fed up to 550 mg per kg daily for 10 consecutive days, or in pregnant hamsters fed up to 300 mg per kg daily for 5 consecutive days.

Methyl paraben or propyl paraben, dissolved in propylene glycol and applied to the skin of 50 human subjects every other day for 10 applications, produced no irritation at the 5 percent level (methyl) or 12 percent level (propyl). In man, 0.1 to 0.3 percent aqueous solutions of methyl paraben, instilled into the eyes of more than 100 patients, produced moderate hyperemia, slight lacrimation, and a sensation of burning which disappeared within one minute. Repetition of this procedure several times a day resulted in no complaints from the 100 subjects. It was noted in 1969 that eight cases of contact dermatitis due to the parabens had been reported in the U.S. scientific literature.

The following long-term studies of the feeding of the parabens are relevant.

Weanling Wistar rats, fed 0.9 to 1.2 g per kg per day for 96 weeks of either methyl or propyl paraben, remained indistinguishable from the controls. Autopsies revealed no pathology in kidney, liver, heart, lung, spleen, or pancreas. When dosage of either compound was increased about four times, rats showed a slower rate of weight gain than the controls. The authors estimated that the toxic threshold for rats of both methyl and propyl paraben is at least 3,000 mg per kg per day. In mice, the same authors stated, "the doses required to produce toxic effects are so large as to make it difficult to obtain an entirely satisfactory dosage-response curve".

Propyl paraben, fed to rats over an 18 month period at 150 mg per kg per day, resulted in no ill effects and "some evidence of growth stimulation". When fed at a level of 1,500 mg per kg per day there was a decrease in growth rate, "but no irregular pathological changes could be found." No experiments were reported for methyl paraben, but ethyl paraben, fed at the foregoing levels paralleled the experience with propyl paraben. In another study, weanling rats, fed as much as 1,430 mg per kg per day of a mixture of 60 parts propyl paraben and 40 parts ethyl paraben for 18 months, showed growth rates comparable to the controls and "histological examination revealed no significant pathological differences among the test and control rats."

No oral carcinogenicity studies of the parabens have been reported. There are two reports of carcinogenicity studies by other routes of paraben administration. Methyl paraben, dissolved in polyethylene glycol and introduced twice weekly into the vaginas of weanling mice for 18 months, did not initiate carcinomas. In other tests on mice, methyl paraben administered intravenously or subcutaneously exhibited no carcinogenic activity.

The available information reveals that there are no short-term toxicological consequences in the rat, rabbit, cat, dog, or man; and no long-term toxicological consequences in rats, of consuming the parabens in amounts greatly exceeding those currently consumed in the normal diet of the U.S. population. There is no evidence that consumption of the parabens as food ingredients has had an adverse effect on man in the 40 years they have been so used in the United States.

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 Research 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 methyl and propyl paraben that demonstrates a hazard to the public when they are used at current levels or at levels that may reasonably be ex-

pected in the future. Based upon his own evaluation of this information, the Commissioner concurs with this conclusion.

Copies of the Scientific Literature Review on the parabens, the data on the teratology experiments, and the report 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(s), 409(d), 701(a), 52 Stat. 1055, 72 Stat. 1787; 21 U.S.C. 321(s), 348(d), 371(a)) and under authority delegated to him (21 CFR 2.120), the Commissioner proposes that Part 121 be amended as follows:

§ 121.101 [Amended]

1. By revising the introductory text of § 121.101(d) to read as follows:

Substances that are generally recognized as safe for their intended use within the meaning of section 409 of the act are as follows. When the status of a substance has been reevaluated and affirmed as GRAS or delisted from this paragraph, an appropriate explanation will be noted, e.g., "affirmed as GRAS," "food additive regulation," "interim food additive regulation," or "prohibited from use in food," with a reference to the appropriate new regulation. Such notation will apply only to the specific use covered by the review, e.g., direct human food use and/or indirect human food use and/or animal feed and pet food use, and will not affect its status for other uses not specified in the referenced regulation pending a specific review of such other uses.

2. By amending the heading for the column "Limitations or restrictions" in § 121.101(d) to read "Limitations, restrictions or explanations", and by amending subparagraph (2) of paragraph (d) by revising the text in the "Limitations, restrictions or explanations" column for the items "Methyl paraben (methyl-p-hydroxybenzoate)" and "Propyl paraben (propyl-p-hydroxybenzoate)" to read as follows:

§ 121.101 Substances that are generally recognized as safe.

(d)

Product	Tolerance	Limitations, restrictions or explanations
Methyl paraben (methyl-p-hydroxybenzoate).	0.1 percent	Affirmed as GRAS § 121.104(g)(1).
Propyl paraben (propyl-p-hydroxybenzoate).	0.1 percent	Affirmed as GRAS § 121.104(g)(2).

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3. By adding a new section to Subpart B as follows:

§ 121.104 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.

(b) Any use levels included in this section represent maximum use levels under current good manufacturing practices. This section does not authorize addition of any level of an ingredient to a specific food above the amount reasonably necessary to accomplish the intended effect.

(c) The listing of a food ingredient in this section does not authorize the use of such substance in a manner that may lead to deception of the consumer or to any other violation of the act.

(d) The listing of more than one ingredient to produce the same technological effect does not authorize use of a combination of two or more ingredients to accomplish the same technological effect in any one food at a combined level greater than the highest level permitted for one of the ingredients.

(e) If the Commissioner of Food and Drugs is aware of any prior sanction for use of an ingredient under conditions different from those proposed to be affirmed as GRAS, 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 prior sanction in response to the proposal.

(f) The label and labeling of the ingredient and any intermediate mix of the ingredient for use in finished food shall bear, in addition to the other labeling required by the act:

(1) The name of the ingredient.

(2) A statement of the concentration of the ingredient in any intermediate mix.

(3) Adequate information to assure that the final food product may comply within any limitations prescribed for the ingredient.

(g) The following direct human food ingredients have been affirmed as GRAS:

(1) *Methyl p-paraben*. (1) Methyl paraben is the chemical methyl-*p*-hydroxybenzoate, produced by esterification of *p*-hydroxybenzoic acid.

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

(iii) The ingredient is used as a preservative.

(iv) The ingredient is used in food at levels not to exceed good manufacturing practices. Current good manufacturing practice results in a maximum level of 0.1 percent in food.

(2) *Propyl p-paraben*. (1) Propyl paraben is the chemical propyl-*p*-hydroxybenzoate, produced by esterification of *p*-hydroxybenzoic acid.

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

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

(iii) The ingredient is used as a preservative.

(iv) The ingredient is used in food at levels not to exceed good manufacturing practices. Current good manufacturing practice results in a maximum level of 0.1 percent in food.

The Commissioner hereby gives notice that he is unaware of any prior sanction for the use of these ingredients in food under conditions different from the 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, Room 8-88, 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.

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