EVALUATION OF THE HEALTH ASPECTS OF METHYL PARABEN AND
PROPYL PARABEN AS FOOD INGREDIENTS

DECEMBER 1972

Prepared for
Bureau of Foods
Food and Drug Administration
Department of Health, Education, and Welfare
Washington, D. C.

Contract No. FDA 72-85
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Life Sciences Research Office
Federation of American Societies
for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014
NOTICE

This report is one of a series of evaluations of the health aspects of the Generally Recognized as Safe (GRAS) food substances that are being made by the Life Sciences Research Office of the Federation of American Societies for Experimental Biology under contract with the Food and Drug Administration of the U.S. Department of Health, Education, and Welfare. The Federation recognizes that the safety of GRAS substances is of national significance, and its resources are particularly suited to marshalling the opinions of knowledgeable scientists to assist in these evaluations. The Life Sciences Research Office, established in 1962 to make scientific assessments in the biomedical sciences, is conducting these studies.

Qualified scientists were selected as consultants to make a continuing review, analysis, and evaluation of the available information on each of the GRAS substances. These scientists, designated the Select Committee on GRAS substances, were chosen for their competence and judgment with due consideration for balance and breadth in the appropriate professional disciplines. Members of the Select Committee on GRAS Substances who have contributed to this report are named in Section VII. The Select Committee's evaluations are being made independently of FDA or any other governmental or nongovernmental group.

These reports are approved by the Select Committee prior to submission to FDA. Although most LSRO consultants are members of FASEB constituent societies, the reports do not necessarily reflect the views of the Federation as a corporate body or carry the endorsement of the members of its constituent societies.

[Signature]
C. Jelleff Carr, Ph.D., Director
Life Sciences Research Office
FASEB
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I. INTRODUCTION

Under the terms of FDA Contract 72-85, dated March 30, 1972, FASEB's Life Sciences Research Office was requested to evaluate the health aspects of using methyl paraben and propyl paraben as food ingredients, primarily on the basis of information contained in a monograph summarizing the world's scientific literature from 1920 through 1970, and in supplemental documents available as of December 1972. The LSRO Select Committee on GRAS Substances has reviewed these materials, and submits its interpretation and assessment in this report, which is intended for the use of FDA in determining the future status of methyl paraben and propyl paraben under the Federal Food, Drug, and Cosmetic Act.

II. BACKGROUND INFORMATION

Methyl paraben and propyl paraben are, respectively, the methyl ester and propyl ester of p-hydroxybenzoic acid. Neither occurs naturally. They are produced commercially by esterification of p-hydroxybenzoic acid (1,2).

The Food Chemicals Codex (3) specifies that each of the food grade parabens should contain not less than 99 percent of the appropriate ester, not more than 3 ppm arsenic, and not more than 10 ppm heavy metals (as lead).

The parabens have been used in foods for more than 40 years because of their antimicrobial activity, particularly against molds and yeasts (5). Antimicrobial activity of the parabens increases as the chain length of the ester group increases (2,4), but since solubility decreases with increasing chain length, the lower esters (methyl and propyl) are the practical choices for use in foods. The parabens are also useful in extending upward the limiting pH for the effective use of benzoic acid as an antimicrobial agent (2).

The parabens are present in amounts ranging from 0.1 to 0.00001 percent (methyl paraben) and 0.1 to 0.00002 (propyl paraben) in the following categories of foods arranged in decreasing order of paraben content: Processed vegetables, baked goods, fats and oils, seasonings, sugar substitutes, frozen dairy products, processed fruit, soft candy, gelatin puddings, other grain products, nonalcoholic beverages, alcoholic beverages, cheese, and sweet sauces. There are very minor variations from this order, depending on whether the methyl or propyl ester is used. Methyl paraben is not reported to be used in fats and oils, processed fruit, or alcoholic beverages (5).

The Food and Drug Administration's GRAS list indicates a tolerance of 0.1 percent for both methyl and propyl paraben but no other limitations or restrictions (6). FDA also lists both methyl and propyl paraben
among the synthetic flavoring substances and adjuvants that may be safely used in food in the minimum quantity required to produce their intended effect, and otherwise in accordance with all the principles of good manufacturing practice (27).

The total poundage of the parabens used in foods in 1970 is reported to be approximately 16 times (methyl paraben) and 30 times (propyl paraben) that used in 1960 (5). However, there is no information now available to the Select Committee that permits it to determine the extent to which there has been significant change in the paraben content of the foregoing food categories over the past decade.

III. CONSUMER EXPOSURE DATA

A National Research Council subcommittee (5) has supplied the following information on the possible daily human intake of methyl and propyl paraben in the total diet, by individuals in various age groups. The Select Committee has converted these figures to possible intakes per kilogram of body weight.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Possible daily intake</th>
<th>Per kilogram of body weight*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Average</td>
</tr>
<tr>
<td>Methyl:Propyl</td>
<td></td>
<td>mg</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Maximum</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>6-11 months</td>
<td></td>
<td>49</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>12-23 months</td>
<td></td>
<td>93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>2-65+ years</td>
<td></td>
<td>222</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

*Calculations based on an average weight of 60 kg for an adult (7) and the following estimated weights of infants by age groups: 0-5 mos., 5 kg; 6-11 mos., 8 kg; and 12-23 mos., 11 kg (8).

It is recognized that the figures calculated for the daily intake of the parabens per kg of body weight in the age group 2-65+ years could be deceptively low, since individuals from age 2 to maturity will obviously weigh less than 60 kg; thus the daily intake of parabens per kg for children could be significantly higher than the figure indicated. For example, a child weighing 20 kg could consume, on the average, 12 mg of propyl paraben per kg rather than 4 mg, and at a maximum, 19 mg per kg per day rather than 6 mg.
However, such deviations from the figures in the table must also be considered in respect to total production and use of the parabens. The data developed by the NRC subcommittee are based on (a) a survey of the frequency of eating various food products, (b) a determination of the portion size of these food products, and (c) a survey of food producers to determine the percentage use of parabens in these food products (5). The NRC subcommittee has pointed out that its calculations of intakes in most cases are overstated, often by considerable margins.* That this is undoubtedly true in the case of the parabens is borne out by the following calculation: Other NRC data show that the use of the parabens for food purposes in the United States was 9,042 pounds or 4,110 kg (methyl paraben) and 4,031 pounds or 1,832 kg (propyl paraben) in 1970 (5). It is stated that each of these reported figures comprises between 60 and 70 percent of the total actual poundage used as food. On the basis of 60 percent adjusted to 100 percent (6,850 kg of methyl paraben, 3,054 kg of propyl paraben) and a U.S. population of 200 million, the per capita per day average intake would be 0.09 mg for methyl paraben and 0.04 mg for propyl paraben. This means that not nearly enough of the parabens is used by the food industry to permit daily human intakes as high as is indicated in the foregoing table. For example, the average per capita daily intake of 222 mg of methyl paraben indicated in the table would require the use of 16 million kg, or 35 million pounds, of the chemical annually.

In the light of these considerations, therefore, the Select Committee regards the figures given in the table as levels that are highly unlikely to be achieved by any of the age groups.

IV. BIOLOGICAL STUDIES

Studies in rats, rabbits, dogs, cats, and man show that methyl and propyl paraben are absorbed from the gastrointestinal tract and metabolized (9-15). 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.

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*An explanation for such overstatements is detailed in the section, "Significance and Use of Data in Safety Evaluations," of the NRC subcommittee's report (5). The Select Committee finds this explanation reasonable and concurs in the first recommendation in Section XII of the same report, that "In order to conduct a more accurate survey on the intake of substances used in food processing, food consumption data collected specifically for this purpose are needed."
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 (11,12,13).

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 (14).

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 within 12 hours (14). 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 (15).

Relevant short-term animal 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 \(LD_{50}\) of both methyl paraben and propyl paraben for the mouse is reported to be greater than 8,000 mg per kg (16). The oral \(LD_{100}\) 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 6,000 mg per kg for the rabbit and 3,000 to 4,000 mg per kg for the dog (17).

Dogs fed as much as 1000 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 (9). 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 2000 mg per kg per day of methyl paraben and at 4000 mg per kg per day of propyl paraben (18).

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" (19).

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 3000 mg per kg per day (18).
One cat, fed methyl paraben at a dosage of 500 mg per kg per day for 6 days, exhibited nausea, vomiting, and general malaise within 15 minutes of dosage and remained in this condition throughout the experiment (18).

A human volunteer, ingesting 2000 mg of methyl paraben daily for one month, was unaffected. Similarly, a human volunteer ingesting 2000 mg of propyl paraben daily for one month exhibited no visible toxic effects (15). One experimenter reported that he ingested 2000 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" (20).

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 (26).

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) (9). 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 (21). It was noted in 1969 (22) 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 3000 mg per kg per day (9). 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" (9).

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" (16). When fed at a level of 1500 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 1430 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 (23).

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 (24). In other tests on mice, methyl paraben administered intravenously or subcutaneously exhibited no carcinogenic activity (25).

Tests of the parabens for mutagenicity have not been reported.

V. OPINION

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.

In the light of the foregoing, the Select Committee concludes that:

There is no evidence in the available information on the two parabens, methyl and propyl p-hydroxybenzoic acid, that demonstrates a hazard to the public when they are used at levels that are now current or that might reasonably be expected in future.
VI. REFERENCES CITED


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Report submitted by:

January 22, 1973

Date

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Select Committee on GRAS Substances