EVALUATION OF THE HEALTH ASPECTS OF BENZOIC ACID
AND SODIUM BENZOATE AS FOOD INGREDIENTS

JANUARY 1973

Prepared for

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

(This document has not been approved for public release.)

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Life Sciences Research Office
Federation of American Societies
for Experimental Biology
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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 (LSRO) of the Federation of American Societies for Experimental Biology (FASEB) 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.

C. Jeliffe Carr, Ph.D., Director
Life Sciences Research Office
FASEB
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I. INTRODUCTION

Under the terms of FDA Contract 72-85, FASEB's Life Sciences Research Office was requested to evaluate the health aspects of using benzoic acid and sodium benzoate as food ingredients, primarily on the basis of information contained in a monograph furnished by FDA (1), summarizing the world's scientific literature from 1920 through 1970, and in certain supplemental documents available as of January, 1973. Benzoic acid and sodium benzoate are food substances that have been generally recognized as safe (GRAS) under the provisions of Section 121.101 of the Code of Federal Regulations (21 CFR 121.101, revised January 1, 1972).

As indicated in the Food, Drug and Cosmetic Act (21 USC 321(s)), GRAS substances are exempt from the requirement of premarking clearance for food additives. It is stated in 21 CFR 121.1 that GRAS means general recognition of safety by experts qualified by scientific training and experience to evaluate the safety of substances on the basis of scientific data derived from published literature. This section of the Code also indicates that expert judgment is to be based on the evaluation of results of credible toxicological testing, or for those substances used in food prior to January 1, 1958, on a reasoned judgment founded in experience with common food use, and is to take into account reasonably anticipated patterns of consumption, cumulative effects in the diet, and safety factors appropriate for the utilization of animal experimentation data. It is recognized further (21 CFR 121.3) that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

The Select Committee on GRAS Substances of LSRO is making its evaluations of these substances in full recognition of the foregoing provisions. In reaching its decisions the Select Committee, with the concurrence of FDA, is relying primarily on the absence of substantive evidence indicating the existence of a significant risk to the public health, and realizes that a decision, based on reasoned judgment, is expected even in instances where the available information is qualitatively or quantitatively limited.

In this context, the LSRO Select Committee on GRAS Substances has reviewed the available information on benzoic acid and sodium benzoate and submits its interpretation and assessment in this report, which is intended for the use of FDA in determining the future status of benzoic acid and sodium benzoate under the Federal Food, Drug and Cosmetic Act.
II. BACKGROUND INFORMATION

Benzoic acid, also called benzenecarboxylic acid, has the formula C₆H₅COOH; sodium benzoate, also called benzoate of soda, is the corresponding sodium salt, C₆H₅COONa. Benzoic acid occurs naturally in certain foods such as raspberries, cranberries, prunes, cinnamon, ripe cloves, tea, anise, and oil of lovage; most berries contain about 0.05 percent. Sodium benzoate when added to strongly acid foods is partially converted to benzoic acid (1,2,4,38).

The Food Chemicals Codex specifies that the food grade products should contain not less than 99.5 percent benzoic acid or 99.0 percent sodium benzoate respectively. Maximum limits are specified for arsenic (3 ppm), heavy metals as lead (10 ppm), and for other impurities.

Benzoic acid is used as an antimicrobial agent (2) in amounts ranging from 0.1 to 0.00001 percent in the following categories of foods, arranged in decreasing order of benzoic acid content: condiments and relishes, sugar substitutes (0.08%), imitation dairy products, non-alcoholic beverages (0.02%), soft candy, chewing gum, baked goods (0.001 to 0.0007%), alcoholic beverages, frozen dairy products, fats and oils, gelatin pudding, and cheese (6).

Sodium benzoate is used as an antimicrobial agent (2) in amounts ranging from 0.29 to 0.00004 percent in the following categories of foods, arranged in decreasing order of sodium benzoate content: sweet sauces, baked goods (0.1 to 0.05%), condiments and relishes, processed vegetables (0.1 to 0.08%), seasonings and flavors, jams and jellies, fats and oils, gelatin pudding, confectioners frosting, processed fruit, imitation dairy products, gravies, nonalcoholic beverages (0.06 to 0.04%), fruit ices, milk products, soft candy, frozen dairy products, instant coffee and tea, meat products, breakfast cereals (0.005%), alcoholic beverages, hard candy, and cheese (6).

It is noted that the Federal Food and Drug Administration's GRAS list indicates a tolerance in foods of 0.1 percent for benzoic acid and sodium benzoate (41). As is indicated in the foregoing paragraph, only one category of foods, sweet sauces, appears to exceed this tolerance. U. S. Department of Agriculture regulations (42) permit 0.1 percent benzoic acid or sodium benzoate in oleomargarine to retard flavor reversion.

The total poundage of benzoic acid used in foods in 1970 is reported to be 2.1 times that used in 1960 (6). There has been a 1.4 fold increase in use of sodium benzoate in the same decade (6). 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 benzoate content of the foregoing food categories over the past decade.
III. CONSUMER EXPOSURE DATA

A comprehensive survey by a National Research Council subcommittee has provided information on the possible daily human intake of benzoic acid and sodium benzoate in the total diet, as shown in the following tables for individuals in various age groups (6). The Select Committee has converted these figures to possible intake per kilogram of body weight.

<table>
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<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: Av. : Max.</td>
<td>Benzoic acid : Sodium benzoate</td>
</tr>
<tr>
<td></td>
<td>mg : mg</td>
<td>Av. : Max.</td>
</tr>
<tr>
<td>0-5 mos.</td>
<td>0.6 : 1</td>
<td>21 : 0.1</td>
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<tr>
<td></td>
<td></td>
<td>0.2 : 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>6-11 mos.</td>
<td>6 : 21</td>
<td>313 : 0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.6 : 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>39</td>
</tr>
<tr>
<td>12-23 mos.</td>
<td>16 : 46</td>
<td>404 : 1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.2 : 17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>37</td>
</tr>
<tr>
<td>2-65+ yrs.</td>
<td>34 : 87</td>
<td>669 : 0.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.4 : 5.5</td>
</tr>
<tr>
<td></td>
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</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 benzoic acid 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 and thus, the daily intake of benzoic acid or sodium benzoate per kg for children could be significantly higher than the figures indicated. For example, a child weighing 20 kg could consume, on the average, 1.7 mg per kg of benzoic acid rather than 0.6 mg, and at a maximum, 4.4 mg per kg per day rather than 1.4 mg.

However, such deviations from the figures in the table must also be considered in respect to total production and use of benzoic acid and sodium benzoate. The data developed by the National Research Council 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 benzoic acid and sodium benzoate in these food products (6). The NRC subcommittee has pointed out that its calculations of intakes in
most cases are overstated, often by considerable margins.* That this is true in the case of the benzoates is borne out by the following two calculations: Other data collected by NRC indicate that 84,336 pounds (38,334 kg) of benzoic acid and 3,325,062 pounds (1,511,392 kg) of sodium benzoate were used for food purposes in the United States in 1970 (6). It is stated that each of these reported figures comprises between 60 and 70 percent of the total actual poundage used in food. On the basis of 60 percent adjusted to 100 percent (63,890 kg benzoic acid, 2,518,987 kg sodium benzoate) and a U.S. population of 200 million, per capita per day average intake would be 0.9 mg of benzoic acid and 34 mg of sodium benzoate. This suggests that the quantity of benzoates used by the food industry is far below the amount that would allow daily human intakes as high as those indicated in the foregoing table. For example, the average per capita daily adult intake of 34 mg of benzoic acid indicated in the table would require the annual use of 5.5 million pounds (2.5 million kg).

In the light of these considerations, 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, but are more likely to be generous overestimates of the benzoic acid and sodium benzoate content of the human diet.

The Joint FAO/WHO Committee on Food Additives indicates the acceptable daily intake of benzoates (benzoic acid and sodium and potassium benzoate, calculated as benzoic acid) as 0-5 mg per kg (unconditional) and 5-10 mg per kg (conditional) (35). The term "conditional" means that the substance may be employed with an adequate margin of safety provided experts have reviewed the available evidence for the particular use. These figures compare favorably with consumption figures reported in the NRC consumer exposure data (6).

IV. BIOLOGICAL STUDIES

Absorption and Metabolism

Benzoic acid and sodium benzoate have been investigated as food preservatives and as medicinal substances for the past century, and the biochemical mechanisms for their detoxification have been known for 50 years.

*An explanation for such overstatements is detailed in Section XI, "Significance and Use of Data in Safety Evaluations," of the NRC subcommittee report (6). The Select Committee finds this explanation reasonable and concurs in the first recommendation of 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."
Benzoic acid and sodium benzoate are rapidly absorbed by mammals, conjugated with glycine, and rapidly excreted (more than 75 percent within 6 hours) in the urine as hippuric acid (9,10). There is no accumulation of benzoate in the body (10,11). When large doses are given, some of the compound is excreted as the benzyol glucuronide (11,12). The ability to conjugate benzoic acid depends upon adequate liver function and nutritional supply of glycine (13,11). Large doses of benzoic acid or sodium benzoate can produce glycine insufficiency with concurrent decrease in glycine-dependent metabolites.

Short-term Oral Studies

The oral LD$_{50}$ for benzoic acid in the rat is reported to be 2,000 to 2,500 mg per kg (25); for sodium benzoate, 2,100 to 4,070 mg per kg (15,20). The oral LD$_{100}$ for benzoic acid is reported to be 1,520 to 2,000, 2,000, and 2,000 mg per kg for the rabbit, cat and dog, respectively (23). The oral LD$_{50}$ for sodium benzoate in the rabbit and the dog is reported to be 2,000 mg per kg (39). The lethal dose for benzoic acid in sheep is estimated to be 1,000 mg per kg (24).

Mice, fed 80 mg per kg per day of benzoic acid for 8 months, showed significant depression of weight gain, increased liver weights, and enlarged spleens, ovaries, and lungs (25). In another report from the same laboratory (16), mice, administered 80 mg per kg per day of benzoic acid by oral intubation for three months, showed weight gains of 66 to 71 percent of the controls despite equivalent total feed consumption.

Benzoic acid, added to the diet at levels of "1 g% to 10 g%," stimulated growth rate and resulted in rats weighing more than the controls over a span of several weeks. The growth stimulation period was reported to be followed by growth depression but confirmation of this conclusion is not evident in the meager data presented (36).

Male Royal Wistar rats fed a diet containing 3 percent benzoic acid for periods up to 35 days, showed early evidence of toxicity and death of half of the animals in 5 days. Histological examination revealed changes in the ganglia cells of the brain parenchyma. A comparable group of these animals, fed benzoic acid at a level of 1.1 percent failed to show neurotoxic signs or brain pathology. However, the authors interpreted their limited data to indicate that some growth retardation occurred at the 1.1 percent level (22).

Sodium benzoate fed at the high level of 5 percent in the diet of male weanling rats for 3 to 6 weeks elicited no gross toxicity other than growth depression which was largely counteracted by addition of extra glycine to the diet (37).

There are many short-term studies in which sodium benzoate has been fed at a 1 percent level in the diet of rats with no discernible effects (18-20). However, sodium benzoate or benzoic acid fed to rats
with a poor nutritional status at a level of 3 percent of the feed produced growth retardation and some deaths (21,18,22). A 90 day feeding study was carried out on rats exposed to diets containing sodium benzoate at levels of 1, 2, 4, or 8 percent. No adverse effects were observed at the levels lower than 8 percent (15).

Benzoic acid or sodium benzoate was fed to dogs at a level of 1 g per kg per day for 250 days without evidence of an adverse effect on growth, appetite or general physical condition (40).

In an early study (1909), 12 men who drank from 1-2.5 liters of apple juice containing 0.1 percent sodium benzoate complained of burning taste, headache, nausea and vomiting, itching of the skin, sweating, constipation and albuminuria (29). On the other hand there are many accounts in which larger doses of benzoic acid produced no obvious symptoms in man. For example, ingestion of 1 g of benzoic acid in 88 doses over 92 days, or 1 g per day for 88 days, produced no observable untoward effects in human subjects (30). According to Kinsey and Wright (31), massive doses of sodium benzoate (25-60 g per day) were formerly given to rheumatic patients without producing a harmful effect. Doses of 6 g of sodium benzoate have been used to test liver function in many patients (31). Temporary distress due to gastrointestinal irritation, headache, and other central nervous system disturbances are often noted in such tests (11).

Comparisons of toxicity based on these short-term studies show the mouse did not tolerate 80 mg per kg per day of benzoic acid (25), while the rat was not affected by 500 mg per kg per day (17-20), the dog by 1,000 mg per kg per day (40), or humans by 17 mg per kg per day (30).

No evidence of teratogenicity was found in rats administered 510 mg per kg of sodium benzoate by gavage on days 9-11 of gestation (26). Intraperitoneal injection of 1000 mg per kg of sodium benzoate on days 9-11 of gestation produced gross abnormalities and 12 percent fetal mortality (27).

The oral administration of 175 mg per kg of sodium benzoate to pregnant mice and rats daily from day 6 through day 15 of gestation, 300 mg per kg to pregnant hamsters daily from day 6 through day 10 of gestation, and 250 mg per kg to pregnant rabbits daily from day 6 through day 18 of gestation produced no discernible teratologic effects (28).

Long-term Oral Studies

In long-term studies (more than half the life span of the species) benzoic acid has been fed to rats at levels of 1 percent for 4 generations without appearance of abnormality (14).

Feeding studies designed to elicit evidence of mutagenicity of benzoates have not been reported. With respect to carcinogenicity,
sodium benzoate fed to rats at a level of 5 percent in food for 23 weeks, elicited no tumors (37). We are also aware of a report by investigators (16) who dosed mice by oral intubation with 40 mg per kg per day of benzoic acid plus 80 mg per kg per day of sodium bisulfite for 17 months. Of the first generation, 8 out of 100 and of the third generation, 1 out of 8 mice were reported to have malignant tumors. However, it is impossible to assess the validity of the findings or the causative factor(s) from the data given in the report.

Other Relevant Studies

In vitro sodium benzoate at a final concentration of 1.7 M inhibited a variety of enzymes and promoted autooxidation of heme pigments (32). Oral administration of sodium benzoate to rabbits (100 mg per kg) reduced the prothrombin time for 7 days (33). Intubation of 50 mg per kg of sodium benzoate to adult rats caused a decrease in the rate of fat absorption (34).

V. OPINION

There are extensive metabolic data on benzoic acid and sodium benzoate in experimental animals and man. It appears that the rat and human have similar metabolic pathways. Short- and long-term feeding studies, as well as teratological investigations, have also been reported in the rat. Interpolation of the rat data and consumer exposure data indicates that the highest no effect level reported in the long-term laboratory feeding study of sodium benzoate is approximately 180 fold the amount usually present in man's daily diet. The highest no effect level reported in laboratory animal feeding is approximately 90 fold the amount that would be consumed if an individual's diet were to consist only of those foods containing the greatest amounts of sodium benzoate in current usage.

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

There is no evidence in the available information to show that benzoic acid and sodium benzoate as food ingredients constitute a hazard to the general public when 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:

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Select Committee on GRAS Substances