EVALUATION OF THE HEALTH ASPECTS OF POTASSIUM ACID TARTRATE, SODIUM POTASSIUM TARTRATE, SODIUM TARTRATE AND TARTARIC ACID AS FOOD INGREDIENTS

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Prepared for

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

Contract No. FDA 223-75-2004
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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 concerning the health aspects of using the Generally Recognized as Safe (GRAS) or prior sanctioned food substances as food ingredients, being made by the Federation of American Societies for Experimental Biology (FASEB) under contract no. 223-75-2004 with the Food and Drug Administration (FDA), U.S. Department of Health, Education, and Welfare. The Federation recognizes that the safety of GRAS substances is of national significance, and that its resources are particularly suited to marshalling the opinions of knowledgeable scientists to assist in these evaluations. The Life Sciences Research Office (LSRO), established by FASEB in 1962 to make scientific assessments in the biomedical sciences, is conducting these studies.

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

Tentative reports are made available to the public for review in the Office of the Hearing Clerk, Food and Drug Administration, after announcement in the Federal Register, and opportunity is provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the substances covered by the report. The data, information, and views presented at the hearing are considered by the Select Committee in reaching its final conclusions. Reports are approved by the Select Committee and the Director of LSRO, and subsequently reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent society of FASEB) under authority delegated by the Executive Committee of the Federation Board. Upon completion of these review procedures, the reports are approved and transmitted to FDA by the Executive Director of FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of all of the individual members of its constituent societies.

\[Signature\]
Kenneth D. Fisher, Ph.D., Director
Life Sciences Research Office
FASEB
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I. INTRODUCTION

This report concerns the health aspects of using potassium acid tartrate, sodium potassium tartrate, sodium tartrate and tartaric acid as food ingredients. It has been based partly on the information contained in a scientific literature review (monograph) furnished by FDA (1), which summarizes the world's scientific literature from 1920 through 1974.* To assure completeness and currency as of the date of this report, this information has been supplemented by searches of over 30 scientific and statistical reference sources and compendia that are generally available; use of new, relevant books and reviews and the literature citations contained in them; consideration of current literature citations obtained through computer retrieval systems of the National Library of Medicine; searches for relevant data in the files of FDA; and by the combined knowledge and experience of members of the Select Committee and the LSRO staff. In addition, an announcement was made in the Federal Register of January 12, 1979 (44 FR 2687) that opportunity would be provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the health aspects of using potassium acid tartrate, sodium potassium tartrate, sodium tartrate and tartaric acid as food ingredients. The Select Committee received no request for such a hearing.

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321 (s)], GRAS substances are exempt from the premarketing clearance that is required for food additives. It is stated in the Act and in the Code of Federal Regulations (2) [21 CFR 170.3 and 170.30] 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. These sections of the Code also indicate 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. FDA (2) recognizes further [21 CFR 170.30] that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

*The document (PB-241 955/4) is available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.
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 conclusions on safety, the Committee, in accordance with FDA's guidelines, is relying primarily on the absence of substantive evidence of, or reasonable grounds to suspect, a significant risk to the public health. While the Committee realizes that a conclusion based on such reasoned judgment is expected even in instances where the available information is qualitatively or quantitatively limited, it recognizes that there can be instances where, in the judgment of the Committee, there are insufficient data upon which to base a conclusion. The Committee is aware that its conclusions will need to be reviewed as new or better information becomes available.

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

Naturally occurring tartaric acid, HOOC-CHOH-CHOH-COOH, and its salts are generally of the L configuration (based on the absolute configuration of D-glyceral acid). The L forms of tartrates are dextrorotatory in solution and thus, in modern nomenclature, are designated as L(+)-tartrates; in some older publications, they may be designated as d-tartrates. L(+)-tartaric acid may be racemized by boiling in alkaline solution. The meso form of tartaric acid may also be formed by prolonged boiling in an alkaline solution (3). The tartrates used in commerce are obtained as a by-product of wine manufacture and thus have the L(+) configuration (4).

Specifications are described in the Food Chemicals Codex (5) for potassium acid tartrate, sodium potassium tartrate, sodium tartrate and tartaric acid used in food; all are listed as having the L(+) configuration.

Tartrates occur naturally in many fruits, and some foods contain considerable amounts. In one study, Concord grape wine was found to contain 232 mg of tartrates (free acid and salts) per 100 ml (6); while Nagel et al. (7) reported that the tartrate content in 41 different wines ranged from 40 to 370 mg per 100 ml (average about 200 mg per 100 ml) and 40 different musts have tartrate contents ranging from 420 to 1100 mg per 100 ml (average about 800 mg per 100 ml). Based on the study of Nagel et al., (7) a single 200 ml glass of wine would contain, on the average, about 400 mg of tartrates. Mabrouk and Deatherage (8) reported that dried coffee beans contain 0.31 percent tartrate which can be extracted on the first brewing. On this basis, one cup of coffee would contain about 15 mg of tartrates. Unspecified amounts of tartrates were reported to be found in papayas (9) and in pineapple juice (10). Bose and Datta (11) reported that 9.2 percent of the total organic nonnitrogenous acid found in molasses is tartaric acid.

An enzyme from tamarind fruit reportedly catalyzes the epimerization of L(+) tartrate to the meso form (12). Traces of meso-tartrate were found in apples by Kenworthy and Harris (13). Pseudomonas acidovorans produces an enzyme which catalyzes the reversible oxidation of meso-tartrate to oxaloglucolate (14).

Tartrates have a strong tart taste and are used as food ingredients to augment natural and synthetic fruit flavors. Tartaric acid is widely used in grape- and lime-flavored beverages, and in fruit-flavored candies. Tartaric acid and potassium acid tartrate (cream of tartar) are common ingredients of leavening systems including baking powder. Tartaric acid is added to ground dried spices as a stabilizing agent, and to cheeses to prevent discoloration. It serves as a chelating agent in foods containing animal or vegetable fats and as a synergist with antioxidants to prevent rancidity (4).
Tartaric acid is used commercially in such processes as tanning and metal cleaning (3), and is also used by the pharmaceutical industry to form the salts of cationic drugs and as an acidulant in effervescent formulations. Tartrates are reported to have been used as laxatives; one study showed a 10 g dose of sodium tartrate to be an effective laxative (15).

Title 21 of the Code of Federal Regulations (2) lists the following tartrates as multiple purpose GRAS food substances: potassium acid tartrate [21 CFR 182.1077], sodium potassium tartrate [21 CFR 182.1804], and tartaric acid [21 CFR 182.1099]. In addition, Title 21 lists sodium potassium tartrate [21 CFR 182.6804], sodium tartrate [21 CFR 182.6801], and tartaric acid [21 CFR 182.6099] as GRAS sequestrants. Tartaric acid may be used in canned fruits under the "any edible organic acid" clause of 21 CFR 145.3(g).
III. CONSUMER EXPOSURE DATA

A subcommittee of the National Research Council (NRC) surveyed manufacturers by questionnaire concerning the level of addition of GRAS substances to foods in 1970 and estimated the possible average daily intake of these substances by persons in various age groups (16). Based on information supplied by those manufacturers who reported adding the substance to at least one food product in a food category, a weighted mean was calculated for the usual and maximal percentage addition of the substance to foods in that category. Such weighted means for the usual levels of addition of potassium acid tartrate and tartaric acid to foods by categories are presented in Table I. Many foods within these categories probably do not contain added tartrates. No manufacturers reported adding sodium potassium tartrate or sodium tartrate to food.

The NRC subcommittee (16) estimated possible average daily intakes of tartrates (Table II) based on Market Research Corporation of America data of mean frequency of eating foods by food category, U.S. Department of Agriculture data on mean portion size of foods in these categories, and the assumption that all food products within a category contain the substance at the level shown in Table I. Such an assumption is likely to lead to overestimates of intake, and the NRC subcommittee has recognized that in most cases its calculations of possible intakes are overstated, often by a considerable margin.*

An alternative calculation of per capita daily "intakes" of quantities added to foods can be made from data provided in the NRC report (16) on the total poundage of potassium acid tartrate and tartaric acid added annually to processed foods. Based on these data, the daily per capita intake of tartrates added to food in 1970 was about 6 mg each from tartaric acid and potassium acid tartrate (Table III). Such disappearance data are likely to be somewhat in excess of per capita consumption. Nevertheless, the data in Table III suggest considerably lower per capita intakes than those presented in Table II. The Select Committee considers the data in Table III to be more reasonable estimates of average intakes. Table III also provides estimates of the relative amounts of each compound used in 1960 and 1970 in those foods where com-

*An explanation for such overstatements is detailed in Section XI, "Significance and Use of Data in Safety Evaluation." of the NRC subcommittee's report. 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 of the intake of substances used in food processing, food consumption data collected specifically for this purpose are needed."
TABLE I

Level of Addition of Potassium Acid Tartrate and Tartaric Acid To Foods by Food Category (16)

<table>
<thead>
<tr>
<th>Food category</th>
<th>Potassium acid tartrate</th>
<th>Tartaric acid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weighted mean percent</td>
<td>Weighted mean percent</td>
</tr>
<tr>
<td>Baked goods, baking mixes</td>
<td>0.33</td>
<td>0.09</td>
</tr>
<tr>
<td>Grain products such as pastas or rice dishes</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Frozen dairy desserts, mixes</td>
<td></td>
<td>0.20</td>
</tr>
<tr>
<td>Processed fruits, juices and drinks</td>
<td></td>
<td>0.97</td>
</tr>
<tr>
<td>Fruit ices, water ices</td>
<td>0.30</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Meat products</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condiments, relishes, salt substitutes</td>
<td></td>
<td>0.20</td>
</tr>
<tr>
<td>Soft candy</td>
<td>0.02</td>
<td>0.98</td>
</tr>
<tr>
<td>Sugar, confections</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>Jams, jellies, sweet spreads</td>
<td></td>
<td>0.20</td>
</tr>
<tr>
<td>Sweet sauces, toppings, syrups</td>
<td></td>
<td>0.30</td>
</tr>
<tr>
<td>Gelatinns, puddings, fillings</td>
<td>0.08</td>
<td>0.31</td>
</tr>
<tr>
<td>Soups, soup mixes</td>
<td></td>
<td>0.17</td>
</tr>
<tr>
<td>Beverages, nonalcoholic</td>
<td></td>
<td>0.13</td>
</tr>
<tr>
<td>Beverages, alcoholic</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Gravies, sauces</td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>Hard candy</td>
<td>0.28</td>
<td>1.03</td>
</tr>
<tr>
<td>Chewing gum</td>
<td></td>
<td>0.43</td>
</tr>
</tbody>
</table>

Blanks in the table mean that the substance is not added to the foods indicated. Level of addition of potassium acid tartrate and tartric acid is the weighted mean of the levels reported by manufacturers as their usual addition to one or more products in a food category. For discussion of weighted mean see Section X and Exhibit 50 of reference (16).
TABLE II
Possible Daily Intake of Added Potassium Acid Tartrate and Tartaric Acid by Age Group (16)

<table>
<thead>
<tr>
<th>Substance</th>
<th>0-5 months</th>
<th>6-11 months</th>
<th>12-23 months</th>
<th>2-65+ years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg</td>
<td>mg</td>
<td>mg</td>
<td>mg</td>
</tr>
<tr>
<td>Potassium acid tartrate</td>
<td>13</td>
<td>97</td>
<td>196</td>
<td>480</td>
</tr>
<tr>
<td>Tartaric acid</td>
<td>63</td>
<td>697</td>
<td>1288</td>
<td>1703</td>
</tr>
</tbody>
</table>

TABLE III
Quantities of Potassium Acid Tartrate and Tartaric Acid Added Annually to Foods (16)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Relative Amounts used&lt;sup&gt;a&lt;/sup&gt; 1970/1960</th>
<th>Total used (1970)&lt;sup&gt;b&lt;/sup&gt; kg</th>
<th>Per capita daily consumption&lt;sup&gt;c&lt;/sup&gt; mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium acid tartrate</td>
<td>0.8</td>
<td>450,000&lt;sup&gt;d&lt;/sup&gt;</td>
<td>6</td>
</tr>
<tr>
<td>Tartaric acid</td>
<td>0.8</td>
<td>440,000&lt;sup&gt;d&lt;/sup&gt;</td>
<td>6</td>
</tr>
</tbody>
</table>

<sup>a</sup> Based only on the reports from those respondents to the National Research Council (NRC) survey who submitted information for both 1960 and 1970 (16).

<sup>b</sup> Total usage is based on the sum of kilograms used in foods as supplied by NRC and Flavor and Extract Manufacturers' Association (FEMA) recalculated to 100 percent from survey data that the NRC subcommittee estimated to represent about 60 percent of the actual usage.

<sup>c</sup> Based on total consumption 1970 and a U.S. population of 205 million.

<sup>d</sup> A resurvey made in 1975 (43) revealed the use of smaller quantities in processed foods.
parable figures were available. For the period 1960 to 1970, the data indicate that there was a 20 percent decline in the use of potassium acid tartrate and tartaric acid.

In 1974, the FAO/WHO Expert Committee estimated that the acceptable daily intake (ADI) of tartrates from all sources to be 30 mg per kg [calculated as L(+)-tartaric acid] (17).

The Select Committee has found no information regarding the addition of sodium potassium tartrate or sodium tartrate to foods.
IV. BIOLOGICAL STUDIES

Absorption and metabolism

One of the first studies on tartrate metabolism was reported in 1896 by Pohl (18). Following the oral administration of 2.0 to 4.0 g of L(+) sodium tartrate to dogs, it was possible to recover 20 to 40 percent of the administered dose in the urine. Similar results were observed in rabbits, and Pohl (18) anecdotally reported that in man, after the ingestion of 4.0 or 8.0 g of sodium tartrate, tartaric acid could not be found in demonstrable amounts in the urine.

Brion (19) compared 24-hour excretion of the L(+), D(−), DL and meso forms of several tartrates after administration of 2.07 to 4.79 g of the substances by gavage to a single dog weighing 8 kg. Recovery of tartrate in the urine was 25 to 29 percent after administration of L(+) sodium potassium tartrate; 3 to 6 percent after D(−) sodium ammonium tartrate; 25 to 42 percent after racemic (DL) tartaric acid; and 2 to 7 percent after meso-tartaric acid or potassium acid meso-tartrate. Brion (19) concluded that D(−) tartaric acid and meso-tartaric acid are oxidized almost completely in dogs while the L(+) form is metabolized to a lesser extent.

Studies by Neuberg and Saneyoshi (20) in 1911 indicated that when D(−), L(+) or DL-tartaric acid was administered by gavage (5.0 g total) to each of two dogs, from 18 to 24 percent of the D(−), 7 to 31 percent of the L(+) and 21 to 43 percent of the DL tartrate was excreted in the urine during a 48-hour period. The isomeric form of the acid recovered from the urine was the same as that administered.

Simpson (21) demonstrated in rabbits, cats and dogs that from 45 to 88 percent of subcutaneously administered L(+)--tartaric acid was eliminated in the urine of the three species. However, following oral administration, only 0 to 6 percent was recovered from the urine of rabbits and 20 to 30 percent from dogs. Simpson concluded that tartaric acid is not readily oxidized in the tissues but is degraded by bacteria in the intestine.

In 1931, Underhill and associates (22) reported that the metabolic fate of tartrates varied in experimental animals [stereoisomeric form not stated but probably L(+)]. In the rabbit, oral doses of less than 50 mg sodium potassium tartrate per kg body weight were recovered almost completely in the urine but only about 20 percent when 200 mg per kg was given. In the dog, there was about 80 to 100 percent urinary recovery of up to 600 mg per kg doses of subcutaneously injected sodium tartrate or orally administered sodium potassium tartrate. Similar results were found in rats; 60 to 85 percent of an oral dose and 75 to 90 percent of a subcutaneous dose were recovered in the urine.
when 400 mg per kg sodium potassium tartrate was administered. In guinea pigs, there was almost quantitative urinary recovery of parenterally administered sodium potassium tartrate, while only about 12 to 18 percent of the substance was recovered when administered by stomach tube.

The metabolism of sodium potassium tartrate in man was also studied by Underhill and his colleagues (23). When the tartrate [stereoisomeric form not stated but probably L(+)] was administered by mouth in doses of 5.3 to 9.4 g tartaric acid equivalents, about 20 percent was excreted in the urine; none was detected in the feces even after purgative doses. The urinary excretion of the substance was rapid and usually complete within 10 hours. The investigators concluded that in man, tartrate is apparently metabolized during its passage through the alimentary canal, most likely by bacterial action in the large intestine.

In 1933, Finkle (24) examined the metabolism of tartrates in male subjects. Following the oral administration of 2.0 g of L(+) tartaric acid to 12 subjects, 11 to 24 percent was excreted in the urine (average 17 percent). When L(+) sodium tartrate was injected intramuscularly into 10 subjects in doses of 1.0 to 2.0 g, it was eliminated almost quantitatively (85 to 99 percent) within 12 hours. In no case were any traces of tartrates demonstrated in the feces. Finkle concluded the tartrates are not metabolized by the human body and suggested that the portion of tartrate given orally that failed to appear in the urine is destroyed in the intestinal tract by bacterial action.

Pratt and Swartout (25) demonstrated in a series of in vitro tests that sodium potassium tartrate, postassium acid tartrate and tartaric acid are readily degraded by intestinal bacteria.

In 1957, Bauer and Pearson (26) studied tartrate metabolism in man using more specific techniques for tartrate analysis than those of earlier investigators (18,19,22,24). Volunteer subjects (age, sex, or number of subjects not stated) were given 2.0 g oral doses of either D-, L- or DL-tartaric acid. In four trials with the L(+) isomer, 12.2, 7.4, 6.4 and 0.4 percent of the dose was recovered from the urine within 12 hours. One trial with the D(-) isomer gave no detectable urinary tartrate and four trials with the DL racemate gave 4.3, 2.0, 0.9 and 0.5 percent urinary recovery. Tartaric acid was also administered by intramuscular injection in about 750 mg doses. In four trials with the L(+) isomer, there was 16.5, 12.4, 11.7 and 6.35 percent urinary recovery of the injected dose. In two trials with the D(-) isomer, there was 1.86 and 0 percent urinary recovery. Bauer and Pearson (26) concluded that, contrary to earlier reports (23,24), the different forms of tartrate are metabolized in human tissues when given in small amounts.
The Select Committee is unaware of any modern studies using radioactive tracer techniques to measure tartrate absorption or metabolism in animals or humans. Such studies would be helpful in resolving uncertainties concerning the disposition of ingested tartrates.

**Acute toxicity**

In the rat, the oral LD$_{50}$ of sodium tartrate [isomer not stated but probably L(+)] has been estimated to be 1.29 g per kg (27), and that of tartaric acid [isomer not stated but probably L(+)] to be 920 mg per kg when administered by gavage (28). In the latter study, swollen mucosal linings and bloody patches were found in the intestines of the dead rats.

An LD$_{10}$ of 4.37 g per kg for sodium tartrate [isomer not stated but probably L(+)] given orally was determined for mixed strain white mice by Locke et al. (29). In the animals succumbing to the treatment, the intestines were distended with fluid. Ninety percent of the deaths occurred within 24 hours of dosing; there was an average weight loss of 8 percent in the animals surviving the treatment. All of seven white New Zealand male rabbits given single oral doses of 230 to 2760 mg per kg sodium tartrate survived; similarly all of six rabbits survived oral doses of 3.45 to 3.91 g per kg of the substance (29). Four of seven rabbits died following oral administration of 4.6 to 6.2 g per kg of disodium tartrate.

In 1914, Salant and Smith (30) investigated the acute toxicity of L(+) sodium tartrate in rabbits. Oral doses of 3.5 to 4.0 g per kg of L(+) sodium tartrate were without effect and no signs of renal damage were seen after dosing. Oral doses of 5.0 g per kg or more were fatal. No diarrhea occurred in animals dosed with 5.0 to 6.0 g per kg but at necropsy, the intestines were distended and filled with fluid. Diarrhea was found in animals receiving 8 to 10 g per kg of sodium tartrate. When sodium tartrate was introduced intravenously, signs of acute intoxication developed rapidly. The injection of sodium tartrate at the rate of 50 mg per kg per minute required a total dose of 2.2 g per kg to induce acute signs, and 4.2 g per kg to cause death. Sublethal injections of about 400 mg per kg or more caused a transient albuminuria.

Other investigators have studied the toxic effects of intravenously administered tartaric acid in rabbits (31,32). Doses ranging from 300 to 1100 mg per kg have been shown to produce death with convulsions within 8 hours.

Underhill et al. (33) reported that racemic sodium tartrate administered orally and subcutaneously to about 30 fasting, normal and phlorhizinized rabbits, and subcutaneously to two dogs exerted a markedly detrimental influence upon the secretory
efficiency of the kidney, indicated by a greatly reduced excretion of nitrogen and dextrose. Doses of sodium tartrate given subcutaneously ranged from about 400 to 1360 mg per kg in the rabbit and about 900 mg per kg in the dog. Oral doses given to the rabbits ranged from about 1.7 to about 6.0 g per kg. Histological study of the kidneys indicated that tartrate acted specifically upon the epithelium of the convoluted tubules and, to a lesser extent, upon the tubules of the loops of Henle; the glomerules and interstitial tissue remained unharmed. In the disintegrative process, vacuolation occurred first, followed rapidly by necrosis, and finally the dead cells or their debris entirely filled the lumina of the tubules and formed granular and hyaline casts. Histological examination of the liver and adrenals disclosed no abnormalities. The authors found no definite relationship between the dose of tartrate and the extent of damage. The severity of nephritis induced was lessened when the tartrate was administered orally, when the animals were well fed, or when sufficient sodium carbonate was administered to maintain an alkaline urine.

All of three dogs died when given a dose of 15 g of sodium potassium tartrate intraperitoneally (2.0 g per kg assuming 7.5 kg dogs); one dog given about 700 mg per kg survived (34). Nine dogs receiving single doses of 7 to 15 g (about 1 to 2 g per kg) sodium potassium tartrate [isomer not stated but probably the L(+) form] or sodium L(+) tartrate exhibited renal disturbance in the form of urinary changes or severe histological changes. In these studies, one dog received 15 g of sodium L(+) tartrate orally and a second received 7 g sodium potassium tartrate orally. The others received the tartrate by both subcutaneous and intraperitoneal injection. Six of the dogs died 2 to 78 hours after dosing; one survived and two were killed shortly after dosing. Urinary changes consisted of the presence of albumin, depressed excretion of normal urinary constituents and diminished flow of urine or complete anuria. The most striking histological change in the kidney was necrosis of the convoluted tubule, with fatty changes in the loop of Henle and also in the collecting tubules. Exudative glomerular lesions occurred in about half of the animals with severe tubular lesions. The authors found no correlation between the mode of administration and the character of the renal lesion.

Salant and Smith (30) reported that feeding cats doses of 10 to 16 g sodium tartrate per kg caused vomiting and severe diarrhea. A trace of albumin appeared in the urine on the third or fourth day and persisted for one to several days. One cat that received 16 g per kg orally died, while other cats similarly treated survived. Subcutaneous administration of 2.0 g per kg sodium tartrate was fatal to three out of four animals; 1.5 g per kg was fatal for two out of three cats. Albuminuria developed in two cats given 1 g per kg subcutaneously, but no other manifestations were observed.
Short-term studies

Packman et al. (35) maintained 15 male New Zealand rabbits weighing 1 to 3 kg with a diet containing 7.7 percent sodium tartrate [isomer not stated but probably L(+)] for a period of 150 days (about 2.3 g per kg per day). A control group of 15 animals was fed a similar diet with no added tartrate. After 60 days of feeding, the erythrocyte, leucocyte and differential leucocyte counts of both groups were within normal limits; concentrations of blood sugar and nonprotein nitrogen were normal and examination of the urine for appearance, specific gravity, sugar, albumin and microscopic constituents revealed no differences between the two groups. Gross pathologic and histopathologic examination was performed on two animals sacrificed from each group after 30 days feeding, one animal from each group at 60 days, and half the survivors at 100 days. The remaining animals were sacrificed at the conclusion of the study. Food consumption, gross appearance and mortality of the rabbits were unaffected by tartrate feeding and no significant gross or histologic changes attributable to the experimental feeding were found.

Locke et al. (29) found that all of 14 rabbits survived an average of 17 daily consecutive feedings of 460 to 1610 mg per kg (average 1.15 g per kg) of sodium tartrate [isomer not stated but probably L(+)]. Three of six rabbits given daily feedings of 3.45 to 3.91 g per kg sodium tartrate died. The rabbits which survived the treatment underwent about 19 consecutive daily feedings, while the animals that died during treatment succumbed after an average of about six consecutive daily feedings.

Krop and Gold (36) gave four dogs a daily oral dose of 990 mg per kg of tartaric acid for periods of 90 to 114 days. Casts were found in the urine of three of the dogs; the blood chemistry remained normal except in one animal in which azotemia developed, with death in 90 days. Weight changes varied from a gain of 30 percent to a loss of 32 percent. Sections of liver, kidney and lung of the dog which died were subjected to histological examination and a fairly advanced renal tubular degeneration was observed.

Long-term studies

In a 2-year feeding study with rats, groups of animals were equally divided between the sexes and were maintained on a basal ration supplemented with 0.1, 0.5, 0.8 or 1.2 percent tartaric acid (100, 500, 800 and 1200 mg per kg body weight) (37). Twenty-four animals were included in each group; the control group, consisting of 48 animals, received no added tartrates. No differences were noted between the treated animals and the controls in food consumption, body weight gain or mortality. At the end of the 2 years, all the surviving animals were sacrificed. Microscopic examination performed on lungs, heart, liver, spleen, pancreas, stomach, small intestine, kidneys, adrenals, testes, colon, bone marrow, leg bones, leg muscles, lymph nodes, uterus, ovaries, thyroid, and parathyroid
of the treated rats revealed no changes induced by tartaric acid. The incidence of tumors and of spontaneous diseases was unaffected by the oral consumption of tartaric acid in this experiment.

Teratogenicity

The teratogenic potential of L(+) tartaric acid was studied in female mice, rats, hamsters and rabbits (38). Tartaric acid was given daily by oral intubation beginning on the sixth day of gestation; doses ranged from 2.7 to 274 mg per kg in mice, 1.8 to 181 mg per kg in rats, 2.3 to 225 mg per kg in hamsters, and 2.2 to 215 mg per kg in rabbits. The mice and rats received the treatment for 10 days, the hamsters for 5 days, and the rabbits for 15 days. During the test period, the animals were observed daily for appearance and behavior, and the animals were weighed periodically. On days 14, 17, 20 and 29, the hamsters, mice, rats and rabbits, respectively, were subjected to cesarean section and the number of implantation sites, resorption sites, and live and dead fetuses recorded. All live pups were weighed and the urogenital tract of each of them was examined. All fetuses were examined grossly for the presence of external congenital defects. The surviving rabbit fetuses were placed in an incubator for 24 hours for evaluation of neonatal survival; one-third of each litter underwent detailed visceral examination and the remaining two-thirds were examined for the presence of skeletal abnormalities. Under the conditions of the test, tartaric acid exhibited no teratogenic activity.

The teratogenic potential of L(+) tartaric acid was also studied in 96-hour chick embryos. Dose levels of 8 mg per kg and above were toxic when injected into the air cell or yolk. Statistical evaluation of the occurrence of abnormalities in tartaric acid treated embryos failed to indicate that the substance was teratogenic (39).

Mutagenicity

The mutagenic potential of L(+) tartaric acid was evaluated in host-mediated, dominant lethal and cytogenetic studies (28). All three studies were carried out using two different tartaric acid dosing schedules. In the first schedule, the animals were given single oral doses of 1.25, 12.5 or 125 mg per kg. In the second schedule, the animals were given single oral doses of 500 or 4000 mg per kg, or five consecutive daily doses of 14.5 g per kg. The host-mediated assays were carried out in male ICR mice using Salmonella typhimurium strains TA 1530 and G-46 and Saccharomyces cerevisiae. Male rats were used in the dominant lethal assay. Results of both the dominant lethal and host-mediated studies failed to provide evidence that tartaric acid is mutagenic. In the cytogenetic studies, 15 male albino rats were used at each dosage level with five animals each sacrificed at 6, 24 and 48 hours after dosing. Metaphase chromosome spreads
prepared from bone marrow cells showed no significant increase
over control in aberrations at any of the dosage levels. Cytoge-
netic studies were also performed in vitro by incubation of
suspensions of human embryonic lung cell line WI-38 for 24 hours
with concentrations of 1, 10 and 100 μg per ml tartaric acid. No
excess of chromosomal abnormalities was observed in cells exposed
to tartrates at any dosage level.

The possible mutagenicity of L(+) potassium acid tartrate
was investigated using microbial assay systems (40). The compound
was not mutagenic when evaluated in the bacterial plate system using
strains TA 1535, 1537 and 1538 of S. typhimurium with and without
tissue activating systems. The compound was also found not to be
mutagenic to S. cerevisiae.

Miscellaneous studies

In 1914, Post (41) gave two patients single oral doses of
about 3.5 g of sodium potassium tartrate [isomer not indicated
but probably L(+) form]; two other patients were administered the
same dosage a second time after a 3-day rest. One of the latter
received a further dose of about 11.5 g 6 days after the second
dose. Two additional patients received two doses of about 5.2 g
given 3 days apart. A seventh patient was given about 3.5 g per
day for 8 days, allowed to rest for 16 days, then given the same
dosage for an additional 9 days. In no case were adverse effects
observed from tartrate administration. Microscopic examination
and tests of the urine for albumin, specific gravity and pH
revealed no changes resulting from tartrate administration.

Barsotti et al. (42) reported on the occupational exposure
of workers to atmospheric concentrations of up to 32 mg per cubic
meter of L(+), tartaric acid in a plant engaged in the production
of tartaric acid and its derivatives. Upon examination of 156
workers, nine exhibited moderate reddening and edema of the
ungual vallum and chronic cutaneous ulcers subsequent to small
wounds of the skin. The workers employed in the grinding of raw
materials exhibited symptoms similar to so-called metal fume
fever. Tartaric acid was eliminated in the urine of the workers
in concentrations of up to 600 mg per liter without any obvious
signs of damage to the kidneys.
V. OPINION

Tartrates occur naturally in many fruits and high concentrations are found in wine. Consumer exposure data suggest that about 6 mg each of tartaric acid and potassium acid tartrate added to foods are ingested daily per capita (a total of about 0.2 mg per kg in an adult). The literature indicates that there are no differences in the biological effects of the several tartrates added to food and that their toxicity is dose related. Studies using modern tracer techniques would be helpful in ascertaining the extent of absorption and metabolic fate of ingested tartrates.

Tartrates are reported to elicit nephritic lesions in several animal species, but usually only after parenteral injection of very large doses. Daily ingestion of 2.3 g per kg of body weight per day for 150 days produced no ill effects in rabbits. No toxicity was found in rats ingesting up to 1.2 g per kg of body weight of tartaric acid in the diet daily for 2 years. The daily intake of tartrates added to foods is orders of magnitude below that which could be expected to cause toxicity in man.

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

There is no evidence in the available information on L(+) potassium acid tartrate, L(+) sodium potassium tartrate, L(+) sodium tartrate, and L(+) tartaric acid that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current, or that might reasonably be expected in the future.
VI. REFERENCES CITED


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