EVALUATION OF THE HEALTH ASPECTS OF ACETIC ACID, SODIUM ACETATE, AND SODIUM DIACETATE AS FOOD INGREDIENTS

1977

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.

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 acetic acid, sodium acetate, and sodium diacetate 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 June 3, 1977 (42 FR 28600-28601) 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 acetic acid, sodium acetate, and sodium diacetate as food ingredients. The Select Committee received no requests for such a hearing on acetic acid, sodium acetate, and sodium diacetate.

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 that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

*The document (PB-234 898/5) 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 Select 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 Select 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 Select Committee, there are insufficient data upon which to base a conclusion. The Select 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 acetic acid, sodium acetate, and sodium diacetate and submits its 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

Acetic acid, \(\text{CH}_3\text{COOH}\), is a colorless, volatile liquid at ambient temperatures. The pure compound, glacial acetic acid, owes its name to its ice-like crystalline appearance at 15.6°C (3,4). As generally supplied, acetic acid is a 6N aqueous solution (about 36 percent) or a 1N solution (about 6 percent). These or other dilutions are used in adding appropriate amounts of acetic acid to foods (5,6). Acetic acid is the characteristic acid of vinegar, its concentration ranging from 3.5 to 5.6 percent (7).

Sodium acetate, \(\text{CH}_3\text{COONa}\), exists as colorless transparent crystals or as a granular crystalline powder; it may occur as the anhydrous or trihydrated salt. Sodium diacetate (sodium hydrogen diacetate), \(\text{CH}_3\text{COONa} \cdot \text{CH}_3\text{COOH} \cdot x\text{H}_2\text{O}\), is a hydrated molecular complex composed of sodium acetate and acetic acid. It is a white hygroscopic crystalline solid that partially dissociates to form sodium, hydrogen and acetate ions in aqueous solution (3).

Acetic acid or acetates are present in most plant and animal tissues in small but detectable amounts (8,9). They are normal metabolic intermediates, are produced by such bacterial species as Acetobacter, and can be synthesized completely from carbon dioxide by such microorganisms as Clostridium thermoaceticum (10). The rat forms acetate at the rate of 1 percent of its body weight per day (9). Some typical concentrations of acetic
acid found naturally in foods include 2.8 mg per kg in fresh orange juice (11),
as much as 860 mg per kg in some aged cheeses (12), and 700 to 1200 mg per
kg in wines (13).

Acetic acid is listed in the Code of Federal Regulations (2) for use as
a multiple purpose GRAS food substance [21 CFR 182.1005], as a substance
migrating to food from paper and paperboard products used in food packag-
ing [21 CFR 182.90], and as a substance migrating to food from cotton and
cotton fabrics used in dry food packaging [21 CFR 182.70]. It is also
regulated as an acidifying agent in various cheese products [21 CFR 133.123,
133.124, 133.173, 133.178].

Sodium acetate is listed in the Code of Federal Regulations (2) as a
multiple purpose GRAS food substance [21 CFR 182.1721], and as a sub-
stance migrating to food from cotton and cotton fabrics used in dry food
packaging [21 CFR 182.70]. It is also regulated for various purposes,
such as an additive to boiler water used in the preparation of steam that
will contact food [21 CFR 173.310], and as a buffer that may be used in
artificially sweetened fruit jelly [21 CFR 150.141].

Sodium diacetate is listed in the Code of Federal Regulations (2) as
GRAS for use as a sequestrant [21 CFR 182.6754], and for optional use as
a mold and rope inhibitor in bakery products [21 CFR Part 136].

Acetic acid or vinegar, which contains acetic acid as a natural ferme-
tation product, is used in such foods as catsup, mayonnaise and pickles where
acidity and characteristic taste are either desirable or not objectionable (7).
They also exert concurrent antimicrobial action (14). Among food products
preserved with vinegar are pickled fruits, vegetables, sausages, pigs' feet,
and fungi (15,16). Acetic acid is authorized as a refining agent for separating
fatty acids from glycerol in rendered fats (17). The FAO/WHO Expert Com-
mittee on Food Additives (18) does not distinguish between natural and synthetic
acetic acid, and considers the acceptable daily intake as "not limited." Acetic
acid and its sodium, potassium and calcium salts are authorized without limi-
tation in the Netherlands as food preservatives (19).

Sodium acetate is used as a preservative in various foods (8). Sodium
diacetate is used as an antimicrobial in bread, baked goods and other foods
in the United States because it does not contribute to the undesirable flavor
that effective levels of vinegar or acetic acid would impart (14).

Food Chemicals Codex (3) specifications for food grade acetic acid,
sodium acetate, and sodium diacetate, are given in Table I.
TABLE I
Specifications for Acetic Acid, Sodium Acetate, and Sodium Diacetate (3)

<table>
<thead>
<tr>
<th>Specification</th>
<th>Acetic acid</th>
<th>Sodium acetate</th>
<th>Sodium diacetate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay</td>
<td>≥99.5% CH₃COOH</td>
<td>≥99.0% CH₃COONa</td>
<td>≥38% and ≥41% CH₃COOH</td>
</tr>
<tr>
<td>Arsenic (as As), ppm</td>
<td>≤3</td>
<td>≤3</td>
<td>≤3</td>
</tr>
<tr>
<td>Heavy metals as (Pb), ppm</td>
<td>≤10</td>
<td>≤10</td>
<td>≤10</td>
</tr>
<tr>
<td>Alkalinity, percent</td>
<td>≥0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Readily oxidizable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>substances, percent</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

III. CONSUMER EXPOSURE DATA

A Subcommittee of the National Research Council (NRC) surveyed manufacturers in 1970 concerning the levels of addition of acetic acid, sodium acetate, and sodium diacetate to foods (20). Based on information supplied, weighted means were calculated (Table II) for the usual percentage addition of each substance to foods in several categories.

The NRC Subcommittee estimated possible average daily intakes from Market Research Corporation of America data on the 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 II. However, the NRC Subcommittee has recognized that such an assumption is likely to lead to overestimates of intake and that in most cases its calculations of possible intakes are overstated, often by considerable margins. Because of factors detailed in Section XI of the Subcommittee’s report (20) it stated that the average estimated total dietary intakes are likely to be much higher than would be the intakes achieved through consumption of a diet consisting totally of processed foods to which the substances had been added at the maximum levels.

For persons over two years old, the estimates of possible average daily intakes based on the levels of addition listed in Table II were 2.1 g per day for acetic acid, 234 mg per day for sodium acetate and 316 mg per day for sodium diacetate. These estimates should be viewed in the light of estimates made by the same NRC Subcommittee concerning the total amounts of acetic acid, sodium acetate, and sodium diacetate reported by the manufacturers to be used in foods. As may be seen (Table III), the per capita "intakes" calculated from these data are considerably
### TABLE II

Calculated Level of Addition of Acetic Acid, Sodium Acetate and Sodium Diacetate to Foods by Food Category (20)

<table>
<thead>
<tr>
<th>Food category</th>
<th>Acetic acid Weighted mean percent</th>
<th>Sodium acetate Weighted mean percent</th>
<th>Sodium diacetate Weighted mean percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baked goods, baking mixes</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>0.18</td>
</tr>
<tr>
<td>Breakfast cereals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grain products such as pastas or rice dishes</td>
<td></td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>Fats and oils</td>
<td>1.49</td>
<td>0.10</td>
<td>0.08</td>
</tr>
<tr>
<td>Milk, milk products</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheese</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frozen dairy desserts, mixes</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Processed fruits, juices and drinks</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meat products</td>
<td>0.78</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Condiments, relishes, salt substitutes</td>
<td>13.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft candy</td>
<td>&lt;0.01</td>
<td>0.09</td>
<td>0.08</td>
</tr>
<tr>
<td>Sweet sauces, toppings, syrups</td>
<td>0.01</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Gelatins, puddings, fillings</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soups, soup mixes</td>
<td></td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Snack foods</td>
<td>0.15</td>
<td>0.04</td>
<td>0.01</td>
</tr>
<tr>
<td>Beverages, nonalcoholic</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beverages, alcoholic</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gravies, sauces</td>
<td>0.18</td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>Dairy products analogs</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hard candy</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chewing gum</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Blanks in the table mean that the substance is not added to the foods indicated.
smaller than those estimated on the basis of the assumed levels of addition listed in Table II. The Select Committee believes that the data in Table III are the more reflective of the daily intakes of these substances. It is to be noted that these figures also are probably high, since part of the compounds added to foods remains un consumed in discarded liquids and other wastes.

TABLE III
Quantities of Acetic Acid, Sodium Acetate and Sodium Diacetate Added Annually to Foods and Per Capita Daily "Intakes" Calculated Therefrom

<table>
<thead>
<tr>
<th>Substance</th>
<th>Relative quantities added* 1970/1960</th>
<th>Total quantities added 1970 b</th>
<th>Per capita daily &quot;intake&quot; e</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic acid</td>
<td>1.2</td>
<td>9,200,000 kg</td>
<td>120 mg</td>
</tr>
<tr>
<td>Sodium acetate</td>
<td>1.8</td>
<td>160,000 kg</td>
<td>2 mg</td>
</tr>
<tr>
<td>Sodium diacetate</td>
<td>2.9</td>
<td>100,000 kg</td>
<td>1 mg</td>
</tr>
</tbody>
</table>

* Based only on the reports from those respondents to the National Research Council (NRC) survey who submitted information for both 1960 and 1970 (20).

b Recalculated to 100 percent from survey data that the NRC subcommittee estimated to represent about 60 percent of the actual usage.

e Based on a U.S. population of 205 million.

IV. BIOLOGICAL STUDIES

Absorption and metabolism

Herting et al. (21) introduced doses of up to 400 mg of acetic acid into the pylorus-ligated stomachs of anesthetized Sprague-Dawley rats and measured the disappearance of acetic acid over a six-hour period. The absorption of acetic acid showed a typical log-dose response with 2.0 millimoles (120 mg) being absorbed at the highest dose level. Since a constant amount of glycerol was absorbed under the same conditions regardless of the dose introduced, the authors suggested that glycerol absorption is by passive diffusion while acetic acid may be actively absorbed as well.
Davenport (22-24) found that acetic acid is absorbed more rapidly than hydrochloric acid from the vagally denervated pouches of the oxyntic gland area of dogs' stomachs. He suggested that this is due to the fat solubility of acetic acid and concluded that acetic acid, under the experimental conditions used, caused increased permeability of the gastric mucosa that might lead to mucosal damage.

Flemström and Frenning (25) introduced doses of 170 millimoles (10 g) of acetic acid or sodium acetate into the pylorus-ligated stomachs of anesthetized cats and found that acetate disappeared more rapidly after instillation of acetic acid than of sodium acetate. Acetic acid, but not sodium acetate, increased the ionic permeability of the gastric mucosa.

Barry and Smyth (26) used everted sacs of rat jejunum, both in vivo and in vitro, to study transfer of the sodium salts of acetic, propionic, butyric, valeric, and hexanoic acids across the intestinal mucosa. They concluded that acetate disappears more rapidly from the intestine in vivo than in vitro, the rate being about 440 micromoles (26 mg) per 20 minutes after introduction of 20 millimoles (1.2 g). Rate of absorption was decreased with increasing concentration of the dose introduced.

Medzihradsky and Lamprecht (27) found the peak blood concentration of acetate to be 0.21 mg per ml 60 minutes after oral administration of 300 mg of acetic acid to adult female rats. Intraperitoneal injection of 125 mg of acetic acid resulted in a peak blood concentration of 0.73 mg per ml after 15 minutes. In neither case did elevated blood acetate concentration persist for longer than 120 minutes.

Fonnesu and Ciaranfi (28) fed adult dogs a mixture consisting of bread, milk, lard, meat, and water ad libitum. Forty-five minutes after ingestion, the average acetate concentration in the lymph of 13 animals tested was found to average 18.5 mg per 100 ml compared to 7 to 9.5 mg per ml in venous and arterial blood, indicating that acetate produced during digestion is absorbed through the intestine mainly by the lymphatic route. Jentsch et al. (29) found that about 60 percent (close to the theoretically expected value) of the metabolizable energy of acetic acid was utilized by swine when it was used as a feed supplement under conditions of fat production in full-grown animals.

Information concerning the intermediary metabolism of acetates has been obtained mainly from studies in which acetates were administered parenterally. Acetates serve as precursors for a large number of compounds (9). Only small amounts of acetate injected subcutaneously or intraperitoneally were found by Deuel and Milhorat (30) in the urine of phlorhizinized or normal-fasting dogs. Acetate was also found to be ineffective as a glucose former. The amount of sodium acetate administered ranged from 14.5 to 27.4 g (about 1 to 2 g per kg of body weight) dissolved
in 80 to 140 ml of water. The results suggest that acetate is practically completely utilized in the living mammal.

Nicholas and Thomas (31) found that sodium [1-14C] acetate after intra-peritoneal administration (dose not indicated) was incorporated into cholesterol in the brain and liver of immature rats and guinea pigs. No such incorporation occurred in the adult, however, even after the doses were increased. When administered to pregnant rats and guinea pigs, the labeled carbon crossed the placental barrier and became incorporated into the fetal brain cholesterol. Dhopeswarkar et al. (32) injected sodium [1-14C] acetate into the carotid artery of rats. They observed that fifteen seconds after the injection, radioactivity was found to be incorporated into all major polar lipid fractions of the brain, with phosphatidyl serine the most highly-labeled component. Schambye et al. (33) reported that they obtained radioactivity in milk lactose of goats and cows given sodium [1-14C] acetate intravenously.

In vitro experiments, all conducted with sodium [1-14C] acetate, have also shed light on acetate metabolism. According to Huber et al. (34) acetate was incorporated into the phospholipids of human lymphocytes in vitro; the highest percentage was found in lecithin, phosphatidylethanolamine, and sphingomyelin, and the lowest in lysolecithin. Canine alveolar lung cells incubated with sodium acetate resulted in the labeling of both neutral lipids and phospholipids; phosphatidyl choline was the most highly-labeled phosphatide, and cholesterol was the most highly-labeled neutral lipid (35). Hellig and Savard (36) showed conversion of acetate into squalene, sterols, and progesterone in slices of bovine corpus luteum. Tsai et al. (37) reported that rat testicular tissues converted acetate into squalene, sterols, and steroids. Bloch and Benirschke (38) showed that human adrenal slices from 12- to 20-week-old fetuses synthesized several steroids from acetate. Wilkinson (39) found that saturated and unsaturated fatty acids are among the principal products formed from acetate in human preputial skin and the skin of newborn mice.

Acute toxicity

Smyth et al. (40) found the oral LD50 for acetic acid in rats to be from 3.2 to 3.8 g per kg body weight, and Woodard et al. (41), from 3 to 3.7 g per kg. For mice, Woodard et al. (41) reported the oral LD50 to be from 4.4 to 5.6 g per kg. In the work of Woodard et al., the acetic acid was adjusted to pH 6 to 7 before administration. The intravenous LD50 for acetic acid (probably sodium acetate since dose was adjusted to pH 7.3 with sodium hydroxide) in mice has been reported by Orö and Wretling (42) to be 525 mg per kg. Welch et al. (43) found the LD50 for sodium acetate to be 380 mg per kg in mice.
When Hermann et al. (44) injected 10 ml of 0.25N acetic acid into the jugular veins of rabbits at 10-minute intervals, the lethal dose was found to be 500 mg per kg. The minimum lethal dose for intravenous injection of 1N sodium acetate into the jugular vein of rabbits at a rate of 2 ml per minute was reported by Baratto (45) to be 3.54 g per kg.

A single intraperitoneal dose of 4 meq (240 mg) acetic acid per kg body weight failed to kill mice housed at 23°C, but more than 50 percent of mice receiving the same dosage died when housed at either 5°C or 37°C. Sodium acetate toxicity was not temperature dependent at the same dosage. No explanation of this phenomenon was offered by the authors (46).

Okabe et al. (47) suggested that the physiologically damaging effects of strong acetic acid (10 to 20 percent) may be due in part to corrosive action, especially on the alimentary canal in the case of direct application to the gastric mucosa of cats and rats. These may be compared to effects obtained in humans during suicidal attempts or accidental ingestion of highly concentrated acetic acid mixtures (48-54). While corrosion of the alimentary canal was reported in most cases, the amount consumed as a single dose in these instances should not be compared with the same total amount consumed at lower concentrations, particularly when mixed with other ingredients in the diet over a longer period of time. Under such conditions corrosion of the alimentary canal has not been reported.

**Short-term studies**

Sollmann (55) added acetic acid to the drinking water as the sole source of fluids for rats at concentrations up to 0.5 percent for two to four months. The daily doses were as high as 390 mg per kg body weight. At this level, the appetite and growth were adversely affected, food intake was reduced, but the fluid intake remained about the same. The rats lost 2.6 percent of their body weight per week at this concentration. No fatalities occurred. However, no effect on appetite, consumption of fluid, or growth was noted in concentrations from about 8 to 195 mg per kg of body weight.

Female rats were fed a diet in which acetate constituted 24 percent of the total caloric intake in place of starch and glucose (56). Rats fed the acetate diet showed lower weight gains than rats fed diets containing starch and glucose. However, the digestible, metabolizable, and net energy measurements were not significantly affected.

Mori (57) observed gastric lesions in 10 rats fed for 30 days a diet containing 50 ml glacial acetic acid per kg of rice, or about 4.5 g of acetic acid per kg of body weight per day. A few umbilicate lesions of the gastric mucosa were observed in three rats and a slight thickening of the wall in
the forestomach in another three; the remaining four rats in the test showed no gastric change. When another group of five rats was fed the same diet for 325 days, four of the animals showed umbilicate or hyperkeratotic mucosal lesions of the non-glandular portion of the stomach, accompanied by submucosal inflammatory changes.

Long-term studies

No long-term acetate or acetic acid feeding studies have come to the attention of the Select Committee. However, it is to be noted that consumption of vinegar which contains up to 5.6 percent acetic acid has long been practiced without reported adverse effects in normal individuals.

Special studies

Wiseman and Adler (58) reported a purported case of allergy involving a 35-year-old male with a four-year history of hives, especially on the head, arms, and neck, when exposed to cold. Patch-testing with 0.1 percent acetic acid was negative but became positive if followed by application of an ice cube for 15 minutes. Avoidance of foods containing acetic acid relieved the patient of his recurrent urticaria and mucous membrane hypersensitivity to cold. Tuft and Ettelson (59) reported another case of purported allergy to acetic acid in a 37-year-old male with a 32-year history of nasal blockage, asthma, and headache. Relief from these reactions and from frequent oral cankers was obtained following avoidance of foods containing acetic and citric acids.

Teratologic evaluation of apple cider vinegar was made in rabbits (60). The administration of up to 1.6 g per kg body weight of the test material daily to pregnant rabbits (day 6 through day 18 of gestation) had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls. Sodium acetate displayed no teratogenicity in the developing chicken embryo at levels up to 200 mg per kg of egg when injected into the air cell or yolk of unincubated eggs, or at levels up to 100 mg per kg when injected into the air cell or yolk of eggs after 96 hours of incubation. It displayed no toxicity when injected into the air cell (200 mg per kg) and an LD₅₀ of 91.5 mg per kg when injected into the yolk of unincubated eggs (61).

Sodium acetate was tested for mutagenic activity in a series of in vitro microbial assays using strains TA 1535, 1537, and 1538 of Salmonella typhimurium and strain D4 of Saccharomyces cerevisiae with and without metabolic activation by mouse, rat, or monkey liver homogenates. This substance did not exhibit mutagenic activity in any of the assays employed in this evaluation (62).
Female rabbits given oral doses of 0.1 to 0.2 g per kg body weight of acetic acid twice daily for five months, or 0.1 to 0.7 g per kg body weight of acetic acid in drinking water for 13 months exhibited no tumors (63). Demerec et al. (64) found 0.03 percent acetic acid to produce 8 mutants per $10^8$ E. coli cells with 50 to 100 percent survival, compared to 7 to 10 mutants per $10^8$ cells in the controls. Male albino rats given oral doses of 350 mg per kg body weight of sodium acetate three times weekly for 63 days, followed by a dose of 140 mg per kg three times weekly for 72 days, showed no evidence of tumors when examined histologically after 135 days (65).

V. OPINION

Acetates are common constituents of plant and animal tissues. They are normal metabolic intermediates produced in relatively large quantities during the digestion and metabolism of foods.

Although the Select Committee is not aware of any long-term feeding studies of acetic acid or the acetates, short-term studies have revealed no untoward effects at concentrations far exceeding those consumed in the normal diet and do not suggest that adverse effects might be revealed by longer term studies.

No data on carcinogenic evaluation of acetic acid and the acetate salts have come to the attention of the Select Committee. Limited data indicate that acetic acid is not teratogenic in vivo; sodium acetate is not mutagenic and acetic acid is probably not mutagenic in vitro.

No reports of biological studies on sodium diacetate have been found, but since this substance dissociates in the body to sodium acetate and acetic acid, neither of which elicits adverse effects under current conditions of use, the Select Committee believes that use of sodium diacetate can be considered to be without adverse effects.

In light of these considerations, the Select Committee concludes that:

There is no evidence in the available information on acetic acid, sodium acetate, and sodium diacetate 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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