EVALUATION OF THE HEALTH ASPECTS OF CARBONATES
AND BICARBONATES AS FOOD INGREDIENTS

1975

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.

C. Jelleff Carr, Ph. D., Director
Life Sciences Research Office
FASEB
## CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Introduction</td>
<td>1</td>
</tr>
<tr>
<td>II. Background information</td>
<td>2</td>
</tr>
<tr>
<td>III. Consumer exposure data</td>
<td>3</td>
</tr>
<tr>
<td>IV. Biological studies</td>
<td>8</td>
</tr>
<tr>
<td>V. Opinion</td>
<td>14</td>
</tr>
<tr>
<td>VI. References cited</td>
<td>16</td>
</tr>
<tr>
<td>VII. Scientists contributing to this report</td>
<td>22</td>
</tr>
</tbody>
</table>
I. INTRODUCTION

This report concerns the health aspects of using carbonates and bicarbonates 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 1972.* 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, announcement was made in the Federal Register of August 29, 1975 (40 FR 33917 and 33918) 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 carbonates and bicarbonates as food ingredients. The Select Committee received no requests for such a hearing on carbonates and bicarbonates.

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 Code of Federal Regulations 21 CFR 121.1, revised April 1, 1975 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. FDA recognizes 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 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

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*The document (PB-221 231/4) is available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.
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, aware that biological testing is dynamic, bases its conclusions on information now available; it cannot anticipate the results of experiments not yet conducted or those of tests that may be reconduted, using new technologies. These 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 carbonates and bicarbonates 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

Carbonates and bicarbonates are used in foods as neutralizers and leavening agents. These anions occur in body fluids and tissues as the result of normal metabolic processes and are important in the control of acid-base balance. Their salts are usually colorless or white translucent or transparent crystals, flakes, powders or granules. Except for calcium carbonate, most of the carbonates used in foods are fairly soluble in water. They may decompose in dry and/or moist air with temperature gradients proportionately influencing the rate of degradation.

Potassium carbonate, potassium bicarbonate, calcium carbonate, sodium carbonate, sodium bicarbonate, and sodium sesquicarbonate are GRAS substances under the provisions of the Code of Federal Regulations (2). Ammonium carbonate and ammonium bicarbonate are evaluated in a separate report (3) and magnesium carbonate will be considered in a future report on magnesium salts. Some of the data on ammonium salts and magnesium carbonate are included in this report for comparison. Each of these substances is listed as a miscellaneous and/or general purpose food additive [121.101(d)(8)]. Calcium carbonate is also listed as a nutrient and/or dietary supplement [121.101(d)(5)]. Magnesium and sodium carbonates are listed as substances migrating to food from paper and paperboard products used in food packaging [121.101(h)], and sodium bicarbonate and sodium carbonate are listed as substances migrating to food from cotton and cotton fabrics used in dry food packaging [121.101(i)]. In addition, baking powder is GRAS [121.101(a)]; it commonly contains sodium bicarbonate and may include other carbonate...
salts such as calcium carbonate (4, 5). The Food Chemicals Codex (6) provides specifications for the food grade salts (Table I).

The carbonate salts of manganese, iron, copper, zinc, and cobalt in anhydrous or hydrated form are GRAS substances for addition to animal feeds [I21.101(f)]. These salts are not evaluated in this report.

III. CONSUMER EXPOSURE DATA

A subcommittee of the National Research Council (NRC) surveyed manufacturers by questionnaire concerning the addition of GRAS substances to foods (7). Based on information supplied by those manufacturers who reported adding the substance to at least one food product in a category, weighted means were calculated for the usual and maximal percentage addition of the substance to foods in the categories. For a given category, the mean of the usual addition levels reported by a manufacturer was weighted by the ratio of pounds used by that manufacturer in all categories to the pounds (all categories) used by those manufacturers that reported use in the category. Weighted means of the usual levels of addition are included in Table II. The Select Committee has no information concerning changes in the level of addition of carbonates to foods in recent years.

The NRC subcommittee estimated possible average daily intakes (Table III) from the 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. Such an assumption is likely to lead to overestimates of intake. The NRC subcommittee has recognized that in most cases its calculations of possible intakes are overestimated, often by considerable margins.* Because of factors detailed in Section XI, the subcommittee reported 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 (7).

*An explanation for such overstatements is detailed in Section XI, "Significance and Use of Data in Safety Evaluations", of the NRC subcommittee's report (7). 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."
<table>
<thead>
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<th>Compound</th>
<th>Assay percent</th>
<th>Arsenic ppm</th>
<th>Heavy metals (as lead) ppm</th>
<th>Other impurities ppm</th>
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<td></td>
<td>NH₄HCO₃</td>
<td></td>
<td></td>
<td>Sulfur compounds</td>
</tr>
<tr>
<td>Ammonium carbonate¹</td>
<td>30.0 - 34.0</td>
<td>&gt;3</td>
<td>&gt;10</td>
<td>&gt;50</td>
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<td></td>
<td>NH₃</td>
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<td>Sulfur compounds</td>
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<td>98.0</td>
<td>&gt;3</td>
<td>&gt;30²</td>
<td>&gt;40</td>
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<tr>
<td></td>
<td>CaCO₃</td>
<td></td>
<td></td>
<td>Fluoride</td>
</tr>
<tr>
<td>Potassium bicarbonate</td>
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<td>&gt;3</td>
<td>&gt;10</td>
<td>&gt;10000</td>
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<td></td>
<td>KHCO₃</td>
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<td>Magnesium and alkali salts</td>
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<td>&gt;40</td>
</tr>
<tr>
<td></td>
<td>K₂CO₃</td>
<td></td>
<td></td>
<td>Fluoride</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>99.0</td>
<td>&gt;3</td>
<td>&gt;5</td>
<td>&gt;10</td>
</tr>
<tr>
<td></td>
<td>NaHCO₃</td>
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<tr>
<td>Magnesium carbonate</td>
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<td>&gt;30²</td>
<td>&gt;6000</td>
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<tr>
<td></td>
<td>MgO</td>
<td></td>
<td></td>
<td>Calcium oxide</td>
</tr>
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</table>

¹ Consists of ammonium bicarbonate and ammonium carbonate in varying proportions.
² <10 ppm lead
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<tr>
<th>Food Category</th>
<th>Ammonium carbonate (\text{Weighted mean percent})</th>
<th>Ammonium bicarbonate (\text{Weighted mean percent})</th>
<th>Calcium carbonate (\text{Weighted mean percent})</th>
<th>Magnesium carbonate (\text{Weighted mean percent})</th>
<th>Potassium carbonate (\text{Weighted mean percent})</th>
<th>Potassium bicarbonate (\text{Weighted mean percent})</th>
<th>Sodium carbonate (\text{Weighted mean percent})</th>
<th>Sodium bicarbonate (\text{Weighted mean percent})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baked goods, baking mixes</td>
<td>0.35</td>
<td>0.32</td>
<td>0.23</td>
<td>0.23</td>
<td>0.43</td>
<td>0.63</td>
<td>0.04</td>
<td>0.04</td>
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<td>Breakfast cereals</td>
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<td></td>
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<tr>
<td>Grain products such as pastas or rice dishes</td>
<td>0.06</td>
<td>0.18</td>
<td>&lt;0.01</td>
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<td></td>
<td></td>
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<td>Fats and oils</td>
<td></td>
<td></td>
<td>0.08</td>
<td></td>
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<td>Milk, milk products</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cheese</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Frozen dairy desserts, mixes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
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<td></td>
<td></td>
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<tr>
<td>Processed fruits, juices, and drinks</td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Meat products</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Poultry products</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Eggs, egg products</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Fish products</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Processed vegetables, juices</td>
<td></td>
<td></td>
<td>0.01</td>
<td>***</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Condiments, relishes, salt substitutes</td>
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<tr>
<td>Soft candy</td>
<td>0.07</td>
<td>1.28</td>
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<td>0.39</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sugar, confections</td>
<td></td>
<td>2.33</td>
<td>1.13</td>
<td>0.36</td>
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<td></td>
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<tr>
<td>Jams, jellies, sweet spreads</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Sweet sauces, toppings, syrups</td>
<td></td>
<td></td>
<td>2.50</td>
<td>&lt;0.01</td>
<td>0.02</td>
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<td></td>
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<tr>
<td>Gelatins, puddings, fillings</td>
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<td></td>
<td>1.50</td>
<td>0.92</td>
<td></td>
<td></td>
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<td>0.24</td>
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<tr>
<td>Soups, soup mixes</td>
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<td>0.01</td>
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<tr>
<td>Snack foods</td>
<td>0.10</td>
<td>0.18</td>
<td>&lt;0.01</td>
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<tr>
<td>Beverages, nonalcoholic</td>
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<td></td>
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<tr>
<td>Reconstituted vegetable proteins</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gravies, sauces</td>
<td>0.04</td>
<td>0.02</td>
<td>0.02</td>
<td>0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Dairy products analogs</td>
<td></td>
<td></td>
<td>0.23</td>
<td>0.17</td>
<td>0.04</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hard candy</td>
<td></td>
<td></td>
<td>2.45</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chewing gum</td>
<td>***</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Seasonings and flavors</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baby food, baked goods</td>
<td>0.37</td>
<td>0.20</td>
<td>0.02</td>
<td>0.55</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Baby formulas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Blanks in the table mean that the substance is not added to foods in the categories indicated. Asterisks (***) in the table mean that there were insufficient data on which to base an estimate. Level of addition of carbonates 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 text, also Section X and Table 59 of reference 1.
<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>mg/kg</td>
<td>mg/kg</td>
<td>mg/kg</td>
<td>mg/kg</td>
<td>mg/kg</td>
</tr>
<tr>
<td>Ammonium bicarbonate</td>
<td>13</td>
<td>3</td>
<td>97</td>
<td>12</td>
</tr>
<tr>
<td>Ammonium carbonate</td>
<td>41</td>
<td>8</td>
<td>273</td>
<td>12</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>70.1</td>
<td>14.0</td>
<td>54.5</td>
<td>68</td>
</tr>
<tr>
<td>Magnesium carbonate</td>
<td>8.0</td>
<td>1.2</td>
<td>63.0</td>
<td>8</td>
</tr>
<tr>
<td>Potassium bicarbonate</td>
<td>56.0</td>
<td>11.2</td>
<td>1.2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>15.0</td>
<td>3.0</td>
<td>117.0</td>
<td>15</td>
</tr>
<tr>
<td>Sodium carbonate</td>
<td>7.0</td>
<td>1.0</td>
<td>136.0</td>
<td>6</td>
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</tbody>
</table>

Calculation of mg per kg of body weight was based on an average weight of 60 kg for an adult (8) and the following estimated weights of infants by age groups: 0-5 mo, 5 kg; 6-11 mo, 8 kg; 12-23 mo, 11 kg (9).

*No reported use in regular foods by NRC survey respondents.
The Select Committee believes the average intakes calculated by the NRC subcommittee (Table III) could be achieved only by a small fraction of the population. Overestimation of intakes for the general population is particularly evident with respect to ammonium carbonate, for which the estimate of intake by the NRC subcommittee is 741 mg per day for individuals over 2 years old (Table III) whereas the total annual consumption in 1970 divided by a U.S. population of 210 million is less than 1 mg per day. Average intakes for individuals over 2 years old are more likely to be of the order calculated from the quantities used annually in foods (Table IV).

### TABLE IV

<table>
<thead>
<tr>
<th>Substance</th>
<th>Relative amounts used(^1)</th>
<th>Total used (1970)(^2)</th>
<th>Per capita daily intake(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1970/1960</td>
<td>kg</td>
<td>mg</td>
</tr>
<tr>
<td>Ammonium bicarbonate</td>
<td>2.0</td>
<td>3,200,000</td>
<td>42</td>
</tr>
<tr>
<td>Ammonium carbonate</td>
<td>0.8</td>
<td>24,000</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>1.7</td>
<td>15,000,000</td>
<td>196</td>
</tr>
<tr>
<td>Magnesium carbonate</td>
<td>2.0</td>
<td>380,000</td>
<td>5</td>
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<tr>
<td>Potassium bicarbonate</td>
<td>0.5</td>
<td>7,000</td>
<td>&lt;1</td>
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<td>6.0</td>
<td>1,800,000</td>
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</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>1.8</td>
<td>43,000,000</td>
<td>561</td>
</tr>
<tr>
<td>Sodium carbonate</td>
<td>1.3</td>
<td>16,000,000</td>
<td>209</td>
</tr>
</tbody>
</table>

\(^1\) Based only on the reports from those respondents to the NRC survey who submitted information for both 1960 and 1970 (7).

\(^2\) Total usage is based on the sum of kilograms used in foods as supplied by NRC (National Research Council) and FEMA (Flavoring Extract Manufacturers' Association) recalculated to 100 percent from survey data that the NRC subcommittee estimated to represent about 60 percent of the actual usage.

\(^3\) Based on total consumption 1970 and a U.S. population of 210 million.

In the case of infants less than 6 months old, an overestimate results from values stated as usual additions to infant formulas. On any specified day, if one considers as a group all individuals less than 6 months old, it may be estimated that 60 percent will receive commercially-prepared infant formulas, the remainder being breastfed or receiving fresh or evaporated milk. Approximately 9 percent of all infants less than 6 months old receive milk-free commercially-prepared infant formulas, mostly
soy-isolate-based (10, 11). A few such formulas contain carbonates or bicarbonates. Most milk-based formulas do not contain added carbonate or bicarbonates.

It is not possible to determine the total daily intake of added carbonates and bicarbonates on the basis of the amount used annually because they are frequently used as leavening agents and the added carbonate is no longer present in the consumed food. In addition, the salts evaluated in this report do not represent unique dietary sources of their elements, and other added and naturally occurring sources will need to be considered if total dietary intake becomes a matter for concern. The Select Committee has considered the interaction of added calcium with other nutrients in its report on phosphates (12).

IV. BIOLOGICAL STUDIES

The biochemical role of the bicarbonate salts has been studied for over 50 years. Investigations using radioisotope procedures have educed extensive information concerning their absorption, metabolism, excretion, and control of acid-base balance of the body. The Select Committee has found few reports of experiments expressly designed to determine the oral toxicity, mutagenicity, teratogenicity or carcinogenicity of the various carbonate compounds. Knowledge of specific toxic levels and the effects of long-term feeding on various species of animals is lacking.

A. POTASSIUM CARBONATE AND BICARBONATE

Acute administration data: Orally administered to an unstated number of rats, potassium carbonate had an LD50 of 1.87 g per kg (13). Potassium bicarbonate caused an 80 percent increase in intercalated cells of the collecting tubules of the kidneys of rats 4.5 hours after intubation of 345 mg (14).

Short-term data: Ten chicks fed potassium bicarbonate as a 3 percent supplement to a basal diet for up to four weeks showed no signs of illness, although two chicks developed white liver nodules (15). In other animal studies, 11 lambs fed a concentrated ration supplemented by 2 percent of 1:1 mixture of sodium and potassium bicarbonate for 59 days showed an increase in weight gain, feed consumption and feed efficiency (16).

Special studies: Potassium carbonate in in vitro microbial assays was not mutagenic in assays with Saccharomyces cerevisiae, strain D4 and Salmonella typhimurium, strains TA-1535, TA-1537, and TA-1538. Tissue homogenates for plate and suspension activation assays were prepared from liver, lungs and testes of mice, rats and monkeys (17).
Teratologic evaluation of potassium carbonate was performed in mice and rats (18). The administration of up to 290 mg per kg to pregnant mice and up to 180 mg per kg to pregnant rats for 10 consecutive days (day 6 through day 15 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 group did not differ from the number occurring spontaneously in the sham-treated controls.

B. SODIUM CARBONATE AND BICARBONATE

Acute administration data: The acute oral toxicity of sodium bicarbonate was studied in intubated Wistar SPF rats weighing 100 to 150 g; LD₅₀ levels reported were 8.9 g per kg in fed rats, 7.57 g per kg in fasted rats on wire floored cages, and 8.46 g per kg in fasted rats bedded on wood shavings. Dose volume was influential: the LD₅₀ was 8.39 g per kg in fed rats receiving 20 to 25 ml per kg, compared to 5.85 g per kg in fasted rats receiving 32 ml per kg (19). In another study using 200 g rats, the LD₅₀ levels observed at 20 ml per kg and 50 ml per kg were 5.5 ± 0.6 g per kg and 4.85 ± 0.3 g per kg, respectively (20). Intubation of 290 to 483 mg of sodium bicarbonate caused an 80 percent increase in intercalated cells of the collecting tubules of the kidneys of rats (14).

Metabolism: The intraperitoneal injection of 18 μCi of sodium [¹⁴C]bicarbonate into CFW mice was followed by assays (after 24 and 48 hours and 1, 2, 4, and 12 weeks) of blood, spleen, liver, kidneys, lungs, brain, jejunum, muscle, skin, hair and long bones (21). More than 90 percent of the total radioactivity injected was lost via the respiratory route in one hour. At 24 hours, most of the radioactivity in the blood was in noncarbonate form. Specific activity in long bones paralleled that in the blood for up to 12 weeks. The radioactivity of the compound injected into a pregnant mouse was fixed in the fetal tissues more rapidly than in the maternal tissues. Variable and transient responses in erythrocyte counts and hemoglobin levels in mice to orally administered sodium bicarbonate were reported (22).

Rapid absorption was demonstrated in rats after intraperitoneal injection of less than one mg sodium [¹⁴C]bicarbonate. Expired radioactivity reached a maximum specific activity within 4 to 10 minutes, and by 13 to 16 minutes the specific activity was reduced by half (23, 24). In a further study, rats were fasted for 24 hours and given lactate by stomach tube, followed by five intraperitoneal injections of sodium [¹¹C]bicarbonate made at 30 minute intervals (25). The animals were sacrificed one-half hour later and about 60 percent of the label was accounted for. The livers were removed and the glycogen extracted; 0.3 to 1.1 percent of the administered carbon-11 was present in the glycogen. Urine contained 1.3 percent
of the dose and over 50 percent of the dose was accounted for by respiratory
\[^{11}\text{C}]\text{carbon dioxide. The authors calculated that one out of eight carbon}
atoms present in the glycogen was derived from the bicarbonate carbon.
Sodium bicarbonate has been reported to affect citrate metabolism in the
kidneys of rats (26). An intraperitoneal injection of 672 mg per kg into
four male rats caused a threefold rise in tissue citrate levels of the kidney
and a smaller but significant rise in citrate levels in the liver.

In man, at plasma bicarbonate levels below 24 mM, virtually all
bicarbonate entering the renal tubules is reabsorbed. Above this level the
excess bicarbonate is excreted (27). Oral administration of sodium bicar-
bonate at one g per kg as a single dose increased sodium excretion and
decreased blood chloride concentration and urine chloride excretion (28).
These studies demonstrate that the carbonate and bicarbonate ions enter
and are constituents of the normal metabolic pathways of man.

**Short-term data:** As reported in a preliminary paper, two groups of
22 two-week-old chicks were given water containing 0.6 and 1.2 percent
sodium bicarbonate for varying periods of time (29). Those fed the
1.2 percent level developed lesions of gout (kidneys damaged by accumu-
lation of urate crystals with accumulation of water in these organs and other
parts of the viscera) as early as the first day. The kidneys of chicks
administered 0.6 percent sodium bicarbonate became pale on the first
day but did not develop lesions of gout. An autopsy showed that all chicks
fed the higher level of bicarbonate developed urate crystals in their kidneys
by the third and fourth days. Mature cockerels were not injured by feeding
the 1.2 percent solution, but 2.4 percent caused clinical signs of gout and
death within five days. The investigators inferred that age and severity of
lesions were inversely correlated. In another study of poultry, three two-
week-old ducklings received 2 percent sodium bicarbonate in their drinking
water and died within 3 days; kidney damage was reported (15).

Intravenous administration of sodium bicarbonate over 7 days for an
average total dose of 3.7 g per kg produced no pathological changes in any
of 28 rats (30). The total dose was given in one to seven daily injections,
the average being 3.7 injections. The same investigators reported no
pathological kidney changes in nine rabbits receiving 2.3 g per kg of sodium
bicarbonate intravenously or in four rabbits receiving 6.4 g per kg sub-
cutaneously over a one-week period (30).

Additional effects on metabolism have been reported in rats and
guinea pigs. Intubation of 0.2 to 0.5 g of sodium bicarbonate decreased
the amount of liver glycogen in fasted rats within 3 hours (31). When fed
in the diet, it induced increased excretion of 3-hydroxybutyric acid and
lactic acid in the urine of rats (32). In the guinea pig, sodium bicarbonate
fed for 15 days at a level of 400 mg per kg with ascorbic acid resulted in
an increased concentration of ascorbic acid in the adrenals and livers as compared to controls fed ascorbic acid (33). These observations were apparently not associated with pathologic changes.

The effect of sodium bicarbonate upon gastric secretion was studied in five dogs. Intubation of 75 to 100 mg sodium bicarbonate per kg three times daily increased gastric secretory activity a short time after a meal; later the secretory volume decreased (34). In a 19 kg dog intravenous injection of 27.4 to 42.5 g of sodium bicarbonate induced alkalois and caused a decrease in serum calcium, chloride and phosphorus but with a large increase in total base, sodium, and blood bicarbonate. Intravenous addition of sodium chloride did not alter the severity of the alkalois, and the sodium and total base values were further elevated (35).

Potassium was retained and ammonia formation decreased in a 25-year-old man who consumed 8.4 g sodium bicarbonate daily (122 mg per kg) for six days (36). Six adult humans ingested 120 mg per kg of sodium bicarbonate daily for five days. Urine calcium decreased significantly for all six subjects when compared to that of a similar control diet period (37).

Thirty-three patients with gastric or peptic ulcers were treated via gastric tube with sodium bicarbonate in daily doses of up to 100 g at a constant rate for three weeks (38). All developed alkalois as plasma carbon dioxide content rose. Inulin and endogenous creatinine clearances indicated no impairment of renal function. The glomerular filtration rate increased during treatment, but it tended to drop to subnormal and recover to normal levels when therapy stopped. No renal damage was observed. Large amounts of sodium were apparently retained in an expanded extracellular space. Oral administration of large doses (840 mg per kg per day) to an infant for 8 days also caused sodium retention (39). One 23-year-old patient (54 kg) received a total dose of 3.2 kg sodium bicarbonate over a period of 20 months for treatment of duodenal ulcer, without marked difference in acid-base balance or decrease in urea clearance and with no change in red and white blood cell counts or hemoglobin values (40).

Special studies: The effect of oral and intravenous administration of sodium bicarbonate to dogs was studied. One kidney was surgically removed from each dog for comparison of pre- and post-treatment morphology (41). Nine dogs received gradually increased doses from 5 to 60 g sodium bicarbonate (up to 10 g per kg) per day. Five of these dogs received oral doses for 30 to 114 days. The remaining four dogs received oral doses of sodium bicarbonate daily and intravenous injection each week for a period of 125 to 261 days. Two dogs in the oral dose group survived; the rest died in acute alkalois. Renal lesions of toxicity were hyperemia, edema and protein precipitation in the tubules. The dogs receiving the intravenous supplement had the greatest renal damage.
In humans, sodium bicarbonate temporarily decreased protease and amylase activity when introduced directly into the jejunum in isotonic solution (42). Cardiac and respiratory rate increases associated with hard exercise were more pronounced under the influence of sodium bicarbonate fed to adult men as a single dose (100 mg per kg). Marked diuresis occurred during fatigue (43). Decreased plasma levels and decreased excretion of ascorbic acid in the urine were observed during a two-week study when 15 g of sodium bicarbonate was fed daily to two female subjects on a diet containing 67 mg of ascorbic acid (44). Drug interactions reported included an increased absorption rate of sulfadiazine when taken with sodium bicarbonate on an empty stomach but sodium bicarbonate apparently delayed absorption of sulfadiazine if given after a meal (45).

Sodium bicarbonate was not mutagenic in in vitro assays with Salmonella or Saccharomyces (46). Sodium bicarbonate and sodium carbonate were not teratogenic in mice or rats (47). Sodium carbonate was neither toxic nor teratogenic in the chick embryo at levels up to 200 mg per kg (48).

C. CALCIUM CARBONATE

Metabolism: Studies of metabolism and excretion have included intraperitoneal implantation of 0.40 mCi of calcium $^{14}$C carbonate as a pellet in a male rat (49). About 72 percent of the radioactivity was excreted as respiratory carbon dioxide between 2 and 142 hours after implantation (most after 69 hours). About 30 percent of the dose was recovered in unabsorbed pellet. Urinary radioactivity accounted for 0.27 percent and fecal radioactivity for about 0.07 percent of the dose; 1 percent of the absorbed dose was retained by the tissues. Significant amounts of radioactivity were incorporated into the inorganic fraction of bone and into bone protein, dentin and enamel, as well as in fatty acids, glycerol, hemin, red cell protein, plasma protein, liver and muscle glycogen, muscle protein and the proteins of the testes, thoracic and abdominal viscera; in the kidney, the highest concentration was in the cortex. The same investigators distributed the compound over the peritoneal viscera of a male rat and collected exhaled air. The largest amount of radioactivity in respiratory carbon dioxide was present on the 7th and 8th days; none was detected on the 22nd day.

Calcium $^{14}$C carbonate injected into a rat produced a higher specific activity in the saturated fatty acids than in the unsaturated fatty acids (50). Similar results were obtained with sodium $^{14}$C carbonate. The carbon-14 content of the carboxyl carbon atoms was twice as high as the average for all fatty acid carbon atoms. Five rats were fed $^{45}$Ca calcium carbonate for three days at 3 g per kg of feed (0.3 g per kg body weight) (51). All rats remained healthy; calcium-45 was deposited in the femur, demonstrating the availability of calcium in the carbonate form.
In humans it has been reported that calcium carbonate taken orally in single doses from 16 to 200 mg per kg caused a transient rise in blood serum calcium (52). After 40 g (0.66 g per kg) calcium carbonate was fed daily for 4 days to three adult humans with peptic ulcers, a large reduction of urinary potassium was observed (53).

**Short-term data:** Addition of calcium carbonate to the basal diet at levels of 1 and 3 percent resulted in lower tissue iron values in anemic rats; this was interpreted as a disturbance in the normal concentration of inorganic ions in the principal absorptive portions of the digestive tract (54). Other investigators have shown that low intake of calcium and a high intake of phosphorus can cause impaired iron utilization with anemia (55, 56). Under some circumstances either calcium salts or phosphate salts may improve iron absorption, while an excess of either may inhibit iron absorption.

Calcium carbonate at 7.26 g per pound of flour in an 80 percent bread diet for 10 weeks in anemic rats (about 0.3 g CaCO₃ daily per kg body weight) decreased food consumption and decreased weight gain (57). Even though the treated diet contained supplemental iron, the iron content of the liver decreased and hemoglobin regeneration was retarded; heart weights increased. It was postulated that the calcium saturated the alimentary mucosal cells, presenting a block to the absorption of iron. The calcium:phosphorus ratio of the experimental diet was about 5:1.

Feeding a cariogenic ration consisting largely of coarsely ground corn supplemented with 3 percent calcium carbonate and 2 to 4 I.U. vitamin D for about four months to three groups of weanling rats resulted in marked reduction of weight gain but had no effect on dental caries incidence (58).

In humans, the oral administration of calcium carbonate to 28 peptic ulcer patients at a level of 500 mg per kg per day, divided into hourly doses during waking hours for three weeks, resulted in six patients developing hypercalcemia (five within 72 hours) with nausea, vomiting, anorexia, weakness, lethargy, headache, and dizziness (59). Blood urea nitrogen values increased significantly. After withdrawal of calcium carbonate the serum calcium values returned to normal.

Calcium retention increased 86.3 percent, and urinary calcium output also increased, when a basal diet providing 1 g calcium daily was supplemented with 2.5 g calcium carbonate and fed to 10 men for 10 days. This provided calcium carbonate at 40 mg per kg and a daily calcium intake of 2 g (60).

**Special studies:** Female Swiss mice were bred after one week on diets which were supplemented by 0.5, 1.0, and 2.0 percent of calcium
carbonate (61). First and second litters were studied. The highest levels of calcium carbonate gave a calcium carbonate intake of about 3 g per kg body weight and a calcium:phosphorus ratio of 2.3:1. This diet significantly lowered the number and total weight of the weanling mice and increased the number and proportion of deaths as compared to a control diet. The control diet provided 0.34 percent calcium and a calcium:phosphorus ratio of 0.70:1. The diet having the highest calcium content caused hypertrophy of the heart and a tendency toward decrease in thymus weight in the weanling rats. These changes were prevented by supplementing the maternal diets with iron. It has been pointed out in another report by the Select Committee (12) that an excess of dietary calcium may precipitate a deficiency of zinc and perhaps certain other trace inorganic elements.

D. SODIUM SESQUICARBONATE

No specific biological information on sodium sesquicarbonate is available to the Select Committee.

V. OPINION

The Select Committee is not aware of any long-term experimental studies on chronic administration of any of the carbonate salts. The results of acute toxicity and short-term feeding experiments are not readily extrapolated in determining toxic levels for carbonate salts consumed by humans. Treatment of gastric or peptic ulcers in patients with large amounts of carbonate salts in various forms has been utilized for many years and only rarely have deleterious results of changes of acid-base balance been reported. When the human respiratory and renal functions are normal, the mechanisms for disposing of bicarbonate intake in large amounts through excretion appear to be highly efficient.

Studies of mice suggest that large intakes of calcium carbonate may interfere with reproductive performance. Such effects could be indirectly attributable to certain trace nutrient deficiencies. Comparable intake levels of calcium may occur when calcium carbonate is used for therapeutic purposes but the amounts added to foods in normal manufacturing processes are not high enough to be harmful. While the Select Committee is not aware of any studies on sodium sesquicarbonate per se, reasoned judgment suggests its biochemical conversion and metabolism would be similar to that of sodium carbonate and bicarbonate.

On the consideration of the foregoing, the Select Committee concludes that:
There is no evidence in the available information on calcium carbonate, potassium carbonate, potassium bicarbonate, sodium carbonate, sodium bicarbonate, or sodium sesquicarbonate that demonstrates or suggests reasonable grounds to suspect a hazard to the public when used at levels that are now current or that might reasonably be expected in the future.
VI. REFERENCES CITED


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