EVALUATION OF THE HEALTH ASPECTS OF ALUMINUM COMPOUNDS 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
C. Jelleff Carr, Ph.D., Director
Life Sciences Research Office
FASEB
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I. INTRODUCTION

This report concerns the health aspects of using aluminum compounds 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 1973.* 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 22, 1976 (41 FR 3332 to 3334) 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 aluminum compounds as food ingredients. The Select Committee received no requests for such a hearing on aluminum compounds.

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321(s)], GRAS substances are exempt from the premarking 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 public

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*The document (PB-223 862/4) is available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161
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 reconducted, 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 aluminum compounds 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

Aluminum, the most abundant metallic element in the earth's crust, occurs as the oxide or in combination with other elements. Although abundant in soil, the amount in water is very low because aluminum compounds are readily precipitated from solution or adsorbed on sediments. The aluminum content of various vegetables and plants averages approximately 200 ppm of the dry weight. Some plants are relatively rich in aluminum; for example, tea leaves may range from 100 to 17,000 ppm (1).

Aluminum compounds are used in foods as buffers, neutralizing and firming agents, and for other purposes. The acidic salts are commonly used as leavening acids and alkaline salts are used in cheese manufacture. Certain aluminum compounds are used in the preparation of self-rising flours, prepared food mixes, and frozen bread doughs (2, 3).

The Code of Federal Regulations (4) lists as GRAS the following aluminum compounds:

**Miscellaneous and/or general purpose food additives [21 CFR 121.101 (d)(8)]**

- aluminum ammonium sulfate
- aluminum potassium sulfate
- aluminum sodium sulfate
- aluminum sulfate
- sodium aluminum phosphate
Substances migrating to food from paper and paperboard [21 CFR 121.101(h)]

aluminum hydroxide
aluminum oleate
aluminum palmitate
sodium aluminate
sodium phosphaaluminate

The Code of Federal Regulations (4) also permits the use of aluminum sulfate in amounts not exceeding 2 percent, together with 1-octenyl succinic anhydride, as an esterifying agent for food starch (21 CFR 121.1031). In addition, several aluminum salts are permitted (4) as ingredients in cereal flours and related products (21 CFR Part 15), and in cheeses, processed cheeses, cheese foods, cheese spreads, and related products (21 CFR Part 19).

The Food Chemicals Codex (2) provides specifications for the food grade aluminum salts indicated in Table I. Aluminum hydroxide, aluminum oleate, aluminum palmitate, sodium aluminate, and sodium phosphaaluminate are not listed in the Codex.

The food grade aluminum salts listed in Table I, and the others included in the GRAS list, have the following properties and specifications:

Aluminum ammonium sulfate occurs as colorless crystals, white granules, or powder (2). It is odorless and has a sweetish, strongly astringent taste. It must assay not less than 99.5 percent AlNH₄(SO₄)₂·12H₂O.

Aluminum potassium sulfate occurs as transparent crystals or a white crystalline powder (2). It is odorless and has a sweetish, astringent taste. It must assay not less than 99.5 percent AlK(SO₄)₂·12H₂O.

Aluminum sodium sulfate occurs as an anhydrous white powder or, with 12 molecules of water of hydration, as colorless crystals (2). It is odorless and has a saline, astringent taste. The anhydrous form must assay not less than 96.5 percent AlNa(SO₄)₂ and the crystalline dodecahydrate not less than 99.5 percent AlNa(SO₄)₂ after drying.

Aluminum sulfate occurs as an anhydrous white powder or with up to 18 molecules of water of crystallization (2). The hydrates are shining plates of colorless crystals, are odorless, and taste sweetish or mildly astringent. The anhydrous form must assay not less than 99.5 percent Al₂(SO₄)₃. The hydrate Al₂(SO₄)₃·18H₂O must assay not less than 99.5 percent and not more than the equivalent of 114.0 percent of Al₂(SO₄)₃·18H₂O, corresponding to not more than 101.7 percent of Al₂(SO₄)₃·14H₂O.

- 3 -
<table>
<thead>
<tr>
<th>Product</th>
<th>Composition</th>
<th>Limits of impurities, ppm</th>
<th>Arsenic</th>
<th>Fluoride</th>
<th>Heavy metals$^a$</th>
<th>Lead</th>
<th>Selenium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum ammonium sulfate</td>
<td>$\text{AlNH}_4 (\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$</td>
<td>$\geq 3$</td>
<td>$\geq 30$</td>
<td>$\geq 20$</td>
<td>$\geq 10$</td>
<td></td>
<td>$\geq 30$</td>
</tr>
<tr>
<td>Aluminum potassium sulfate</td>
<td>$\text{AlK(SO}_4)_2 \cdot 12\text{H}_2\text{O}$</td>
<td>$\geq 3$</td>
<td>$\geq 30$</td>
<td>$\geq 20$</td>
<td>$\geq 10$</td>
<td></td>
<td>$\geq 30$</td>
</tr>
<tr>
<td>Aluminum sodium sulfate</td>
<td>$\text{AlNa(SO}_4)_2 \cdot 12\text{H}_2\text{O}$</td>
<td>$\geq 3$</td>
<td>$\geq 30$</td>
<td>$\geq 20$</td>
<td>$\geq 10$</td>
<td></td>
<td>$\geq 30$</td>
</tr>
<tr>
<td>Aluminum sulfate</td>
<td>$\text{Al}_2 (\text{SO}_4)_3 \cdot 18\text{H}_2\text{O}$</td>
<td>$\geq 3$</td>
<td>$\geq 30^b$</td>
<td>$\geq 40$</td>
<td>$\geq 10$</td>
<td></td>
<td>$\geq 30$</td>
</tr>
<tr>
<td>Sodium aluminum phosphate, acidic</td>
<td>$\text{Na}_3\text{Al}_2\text{H}_5 (\text{PO}_4)_8$ or $\text{NaAl}_3\text{H}_4 (\text{PO}_4)_8 \cdot 4\text{H}_2\text{O}$</td>
<td>Approx. compn.</td>
<td>$\geq 25$</td>
<td>$\geq 40$</td>
<td>$\geq 10$</td>
<td></td>
<td>$\geq 30$</td>
</tr>
<tr>
<td>Sodium aluminum phosphate, basic</td>
<td>$\text{Na}_3\text{Al}_2 (\text{OH})_2 (\text{PO}_4)_8 + 30$ percent of $\text{Na}_2\text{HPO}_4$</td>
<td>$\geq 3$</td>
<td>$\geq 25$</td>
<td>$\geq 40$</td>
<td>$\geq 10$</td>
<td></td>
<td>$\geq 30$</td>
</tr>
</tbody>
</table>

$^a$Expressed as lead.

$^b$In Food Chemicals Codex Supplement (5).
Sodium aluminum phosphate, acidic occurs as a white odorless powder(2). It must assay not less than 95.0 percent of NaAl$_3$H$_{14}$(PO$_4$)$_8$.4H$_2$O or not less than 95.0 percent of Na$_3$Al$_2$H$_{16}$(PO$_4$)$_8$.

Sodium aluminum phosphate, basic occurs as a white odorless powder comprised of an autogenous mixture of an alkaline sodium aluminum phosphate [approximately Na$_6$Al$_2$(OH)$_5$(PO$_4$)$_4$], with about 30 percent dibasic sodium phosphate (2). It must assay not less than 9.5 percent and not more than 12.5 percent of Al$_2$O$_3$ after ignition.

Aluminum hydroxide, Al(OH)$_3$, is available as a gel suspension and as the dried gel (6). It contains aluminum oxide (Al$_2$O$_3$) in the form of aluminum hydroxide and the hydrated oxide. The suspension is white and the dried gel is a white, odorless, tasteless, amorphous powder. Medicinally, aluminum hydroxide is used as an antacid.

Aluminum oleate, [CH$_3$(CH$_2$)$_7$CH=CH(CH$_2$)$_7$COO]$_3$Al, occurs as a yellowish, viscid mass (1).

Aluminum palmitate, [CH$_3$(CH$_2$)$_4$COO]$_3$Al, occurs as a white to yellow mass or powder (1).

Sodium aluminate, NaAlO$_2$, occurs as a white granular mass (1).

Sodium phosphoaluminate is a white powder composed primarily of sodium aluminate (hydrated), sodium orthophosphate, and small amounts of sodium carbonate and sodium silicate (7).

III. CONSUMER EXPOSURE DATA

A subcommittee of the National Research Council (NRC) has provided estimates of the total amounts of several aluminum salts added to processed food products in 1970 (8). These data, given in Table II, together with estimates of the relative annual amounts of each used in 1960 and 1970 where comparable figures are available, provide an indication of the trends in use in foods of several of the aluminum salts over a recent ten-year period. No information concerning trends in usage since 1970 is available. It is noted that use of aluminum sodium sulfate and sodium aluminum phosphate increased about threefold between 1960 and 1970. Although use of aluminum potassium sulfate increased nearly 30-fold in the same period, the total amount used in 1970 was still relatively small.

The NRC subcommittee (8) has provided information on the usual use levels of several aluminum compounds in various categories of foods.
<table>
<thead>
<tr>
<th>Substance</th>
<th>Relative amounts used&lt;sup&gt;a&lt;/sup&gt; 1970/1960</th>
<th>Total used&lt;sup&gt;b&lt;/sup&gt; (1970) kg</th>
<th>Per capita daily intake&lt;sup&gt;c&lt;/sup&gt; mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum ammonium sulfate dodecahydrate (5.95 percent Al)</td>
<td>1.0</td>
<td>230,000</td>
<td>3</td>
</tr>
<tr>
<td>Aluminum potassium sulfate dodecahydrate (5.69 percent Al)</td>
<td>28.8</td>
<td>3,800</td>
<td>&lt;1 (&lt;0.1)</td>
</tr>
<tr>
<td>Aluminum sodium sulfate dodecahydrate (5.89 percent Al)</td>
<td>3.4</td>
<td>3,600,000</td>
<td>48 (2.8)</td>
</tr>
<tr>
<td>Aluminum sulfate octadecahydrate (8.10 percent Al)</td>
<td>1.3</td>
<td>510,000</td>
<td>7</td>
</tr>
<tr>
<td>Sodium aluminum phosphate (avg. 6.5 percent Al)</td>
<td>2.8</td>
<td>18,000,000</td>
<td>240 (15.6)</td>
</tr>
<tr>
<td>Total mg Al/person/day</td>
<td></td>
<td></td>
<td>(19.2)</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.

<sup>b</sup> Total used is based on the usage in foods as supplied by the NRC and the Flavoring 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. Figures in parentheses represent Al equivalents in mg.
The subcommittee surveyed manufacturers by questionnaire concerning the addition of aluminum compounds to their processed products, grouped by categories. Based on the information supplied by those manufacturers who reported adding aluminum compounds to at least one food product in a food category, a weighted mean was calculated for the usual percentage addition to foods in that category. The mean usage level reported by a manufacturer was multiplied (weighted) by the ratio of total pounds used by that manufacturer in all categories to the total pounds reported by all manufacturers in all food categories. The weighted means for the percentage of the several aluminum compounds added to each food category are given in Table III. It is to be noted that these weighted means do not express the highest percentage of aluminum compounds added by any manufacturer; they do not indicate which specific foods in a category contain added aluminum compounds; they do not necessarily coincide with the levels used by any one industry in its products in the food categories listed.

The NRC subcommittee (8) has provided information by age groups on the possible average daily human intakes of the various aluminum salts (Table IV). The Select Committee has converted these figures to possible intakes per kg of body weight. Since food consumption data were not requested in the NRC subcommittee survey, intake estimates were derived by utilizing Market Research Corporation data on mean frequency of eating foods by category, USDA data on mean portion size, and by assuming that all food products within a food category contain aluminum compounds at the levels shown in Table III. Because of factors detailed in the NRC subcommittee's report, they believe that their estimated average intakes (Table IV) are likely to be higher than would be the intakes achieved through consumption of a diet consisting totally of processed foods to which the aluminum compounds have been added at maximum levels.

For comparison, the daily intake figures (Table IV) should be considered in respect to the total amounts of the various aluminum salts reported to be added to processed food and the per capita intakes calculated therefrom (Table II). The calculated per capita daily intakes for each of the five aluminum compounds and their aluminum equivalents are consistently smaller than the corresponding figures for the possible average intake of the 2 to 65+ year age group (Table IV). Moreover, Campbell et al. (II) have estimated that daily aluminum intakes resulting from food, water, and cooking utensils can range from 10 to 100 mg. The total estimated per capita daily intake of 19.2 mg of aluminum due to the consumption of foods to which aluminum compounds have been added (Table II), falls within this range, whereas the possible average total adult daily intake of aluminum indicated by the figures in Table IV would be significantly outside this range. The Select Committee considers
<table>
<thead>
<tr>
<th>Food category</th>
<th>Aluminum ammonium sulfate mean percent</th>
<th>Aluminum potassium sulfate mean percent</th>
<th>Aluminum sodium sulfate mean percent</th>
<th>Aluminum sulfate mean percent</th>
<th>Sodium aluminum phosphate mean percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baked goods, baking mixes</td>
<td></td>
<td></td>
<td>1.09</td>
<td>0.16</td>
<td>1.19</td>
</tr>
<tr>
<td>Grain products such as pastas or rice dishes</td>
<td></td>
<td></td>
<td></td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Cheese</td>
<td></td>
<td></td>
<td></td>
<td>2.22</td>
<td></td>
</tr>
<tr>
<td>Meat products</td>
<td>&lt;0.01</td>
<td></td>
<td>&lt;0.01</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Processed vegetables, juices</td>
<td></td>
<td>0.10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condiments, relishes, salt substitutes</td>
<td></td>
<td></td>
<td>0.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gelatins, puddings, fillings</td>
<td></td>
<td></td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reconstituted vegetable proteins</td>
<td>***</td>
<td>***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dairy products analogs</td>
<td>***</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seasonings and flavors</td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

Level of addition of aluminum compounds 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 8.

Blanks in the table mean that the substance is not known to be added to the foods indicated; asterisks mean that (a), the substance is used in a processing phase of the foods indicated, but residual levels in the final food product are negligible or unknown; (b), the substance is used in the foods indicated but usage levels were not furnished by industry; (c) the substance is in the foods indicated but the levels were considered to be reported incorrectly.
<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/kg</td>
<td>mg</td>
<td>mg/kg</td>
</tr>
<tr>
<td>Aluminum ammonium</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>sulfate</td>
<td>(&lt;1)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(&lt;1)</td>
<td>(&lt;1)</td>
<td>(&lt;1)</td>
</tr>
<tr>
<td>Aluminum potassium</td>
<td>*</td>
<td>*</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>sulfate</td>
<td>(&lt;1)</td>
<td>(&lt;1)</td>
<td>(&lt;1)</td>
<td>(&lt;1)</td>
</tr>
<tr>
<td>Aluminum sodium</td>
<td>37</td>
<td>7</td>
<td>277</td>
<td>35</td>
</tr>
<tr>
<td>sulfate</td>
<td>(2)</td>
<td>(16)</td>
<td>(35)</td>
<td>(88)</td>
</tr>
<tr>
<td>Aluminum sulfate</td>
<td>6</td>
<td>1</td>
<td>45</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>(&lt;1)</td>
<td>(4)</td>
<td>(8)</td>
<td>(20)</td>
</tr>
<tr>
<td>Sodium aluminum phosphate</td>
<td>44</td>
<td>9</td>
<td>425</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>(3)</td>
<td>(28)</td>
<td>(60)</td>
<td>(133)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Calculations based on an average weight of 60 kg for an adult (9) and the following estimated weights of infants by age groups: 0-5 mo, 5 kg; 6-11 mo, 8 kg; and 12-23 mo, 11 kg (10).

<sup>b</sup> Figures in parentheses are mg of Al. For percent Al in each see Table II.

*Insufficient data on which to base an estimate.
the figures in Table IV to be overestimates* of the amounts of aluminum present in the diets of the four age groups and regards the intakes given in Table II as more realistic.

IV. BIOLOGICAL STUDIES

Absorption and metabolism

The widespread distribution of aluminum compounds in nature, and hence in many foods, has stimulated considerable interest in the absorption of these substances from the gastrointestinal tract. In addition, the advent of aluminum cooking utensils has resulted in questions on the possible ingestion of aluminum from this source.

Studies in 1929 on man suggested that aluminum ingested from biscuits or pancakes made with "alum-phosphate baking powder" containing aluminum sodium sulfate was not absorbed in the gut to a significant extent, inasmuch as increases in blood levels of aluminum were not detectable, and less than 0.1 percent of the ingested aluminum was excreted in the urine (12). However, more recent investigations employing more sensitive analytical methods, with male Wistar rats fed basal diets containing 170 ppm of aluminum for 8 days, followed by 8 additional days on a diet containing 2,835 ppm of aluminum added as the sulfate, indicated that aluminum retention was twentyfold greater at the higher dose. The higher dose is estimated to be about 200 mg Al per kg per day. About 70 percent of the dose was excreted in the feces. Tissue deposition of aluminum, especially in the liver and femur and to a lesser extent in the kidney was significantly greater at the higher dose level. On the other hand, in Dobrá Voda mice, treated similarly, fecal excretion of aluminum was increased at the higher dose, but urinary excretion and retention were not (13).

The retention of dietary aluminum, though generally small, depends upon the composition of the food. A high fluoride content of food decreases the retention of aluminum, and dietary level of phosphorus is also a controlling

*The NRC subcommittee has also recognized the likelihood that its intake estimates (Table IV) are overstated. An explanation for such overstatements is detailed in Section XI, "Significance and Use of Data in Safety Evaluations," of the NRC subcommittee's report (8). 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."
factor in the retention and toxicity of aluminum salts (14-17). These experiments involved rats fed or intubated daily for several weeks, usually with 150 to 200 mg aluminum per kg of body weight per day as aluminum sulfate, aluminum chloride, aluminum hydroxide, or aluminum oxide.

A metabolic interaction between aluminum and phosphorus compounds occurs in animals. When mice or rats were fed various levels of aluminum chloride in their diet, there was a decrease in retention of phosphorus that correlates inversely with the dose of aluminum (13). A single oral dose of aluminum chloride (188.2 mg of AlCl₃ or 37 mg of Al per kg) to rats caused a significant decrease in absorption of phosphate as measured by radioactivity uptake from phosphorus-32 labeled Na₂HPO₄. In this study evidence was presented to suggest that aluminum salts tend to inhibit phosphorylation mechanisms. There was a reduction of phosphorus-32 incorporation into nucleic acids, and a reduction in the adenosine triphosphate/adenosine diphosphate ratio in the liver (13). Other studies have also shown that aluminum salts can affect enzymes associated with phosphorylation and with carbohydrate metabolism. Oxygen consumption of liver homogenates was 25 percent less in livers taken from rats fed, intubated, or injected intraperitoneally with 150 to 300 mg of aluminum per kg body weight as aluminum sulfate or hydroxide, as compared with livers from control animals receiving no aluminum compounds (18). In chicks, adenosine triphosphate concentrations were reduced in muscle and serum when 25 mg of aluminum hydroxide gel was fed per g of feed (about 4 g per kg of body weight), whereas recovery to normal occurred when extra phosphate was added to the diet (19). Liver glycogen concentration was decreased in rats fed 18 days on a diet containing 200 mg of aluminum per kg of body weight as aluminum chloride (16).

**Antacid uses**

In general, long-term oral administration to humans of aluminum-containing antacids such as aluminum hydroxide for therapeutic or experimental purposes, results in decreased plasma concentration of phosphorus because of decreased phosphorus absorption or increased deposition of phosphorus in bone as an aluminum phosphate compound (20-22). Recently, numerous comments have been published on aluminum toxicity as related to the extensive use of aluminum hydroxide gel as an antacid (18, 23-28). There is no agreement about the clinical hazards of oral use of aluminum hydroxide gel by man, the significance of animal studies, or the interpretation of the concentrations of aluminum found in bone specimens as determined by neutron activation techniques.

After a review and evaluation of the use of antacids, the Food and Drug Administration announced in 1974 that those containing aluminum
compounds are generally recognized as safe for over-the-counter sale and indicated a maximum daily dosage limit of 8 g of aluminum phosphate, equivalent to 1.77 g of aluminum (29). It is to be noted in this connection, however, that substantial intakes of other aluminum salts, such as the chloride or sulfate, can impair retention of phosphorus (13,14).

Acute toxicity

The acute oral and parenteral toxic doses for various aluminum salts in several species of animals are given in Table V. Parenteral injection increases the toxicity of aluminum compounds when administered in high doses daily. The toxicity of absorbed aluminum compounds is increased if renal function is impaired (18).

Short-term studies

Conflicting reports have been published on the short-term toxicity of ingested aluminum salts. Schaeffer and coworkers (32) found gastrointestinal lesions in mice fed an adequate diet including bread, made with aluminum phosphate or alum-phosphate baking powder, for 4 months, at levels equivalent to 1.3 and 4.4 percent aluminum, respectively, in the diet (estimated to be about 2 and 6.5 g Al per kg per day at start of the experiment). Reproductive failure associated with ovarian lesions occurred in all groups fed these very large doses of the aluminum salts. In contrast, Lyman and Scott (33) found no effect on rate of growth, maximum adult size, longevity, kidney function, and reproduction in rats fed a diet containing 2 percent of an aluminum sodium sulfate-calcium acid phosphate baking powder (about 50 mg Al per kg of body weight per day) for 21 months. Similar absence of untoward effects was noted in other rat studies in which diets containing aluminum chloride or a baking powder containing aluminum sodium sulfate (about 80 to 500 mg per kg per day) were fed for periods of 2 to 8 months (34,35).

Berlyne et al. (18) showed that low oral doses of aluminum chloride, sulfate, or hydroxide (equivalent to 150 to 375 mg Al per kg per day), can produce severe toxic manifestations in nephrectomized rats. Thurston and Swales (36) found that phosphate supplementation (levels not indicated) reversed the growth failure and rachitic bone changes in rats associated with aluminum hydroxide feeding (levels not indicated).

In tests performed by Industrial Bio-Test Laboratories, Inc. for the producer of the chemical, microconcretions were observed in the renal tubules of female rats fed basic sodium aluminum phosphate at dietary levels of 0.3, 1.0, and 3.0 percent (about 4 to 40 mg Al per kg body weight per day) for 90 days (37). Similar studies with the same
<table>
<thead>
<tr>
<th>Animal species</th>
<th>Strain and sex</th>
<th>Aluminum compound</th>
<th>Route of administration</th>
<th>Toxicity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>CDE⁵</td>
<td>nitrate·9H₂O</td>
<td>intraperitoneal</td>
<td>LD₅₀ 320 mg/kg (23 mg Al/kg) LD₁₀ 213 mg/kg (15 mg Al/kg)</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Dobrá Voda⁶</td>
<td>chloride</td>
<td>oral</td>
<td>LD₅₀ 770 ± 120 mg Al/kg</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Dobrá Voda⁶</td>
<td>sulfate</td>
<td>oral</td>
<td>LD₅₀ 980 ± 90 mg Al/kg</td>
<td>13</td>
</tr>
<tr>
<td>Rat</td>
<td>Sprague-Dawley⁷</td>
<td>nitrate·9H₂O</td>
<td>intraperitoneal</td>
<td>LD₅₀ 327 mg/kg (24 mg Al/kg) LD₁₀ 240 mg/kg (17 mg Al/kg)</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>chloride</td>
<td>subcutaneous</td>
<td>LD₁₀₀ 7,000 to 8,000 mg/kg (1416-1618 mg Al/kg)</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Weizmann Inst.⁷</td>
<td>chloride</td>
<td>intraperitoneal</td>
<td>LD₁₀₀ 150 mg/kg</td>
<td>18</td>
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<tr>
<td></td>
<td>Weizmann Inst.⁷</td>
<td>chloride</td>
<td>oral</td>
<td>LD₁₀₀ approx. 1100 mg/kg</td>
<td>18</td>
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<tr>
<td></td>
<td>Weizmann Inst.⁷</td>
<td>sulfate</td>
<td>intraperitoneal</td>
<td>LD₁₀₀ 150 mg/kg</td>
<td>18</td>
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<td>Weizmann Inst.⁷</td>
<td>sulfate</td>
<td>oral</td>
<td>LD₁₀₀ approx. 1100 mg/kg</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Weizmann Inst.⁷</td>
<td>hydroxide</td>
<td>intraperitoneal</td>
<td>LD₁₀₀ 150 mg/kg/day</td>
<td>18</td>
</tr>
<tr>
<td>Guinea pig</td>
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<td>subcutaneous</td>
<td>LD₁₀₀ 5,000 to 7,000 mg/kg (1011-1416 mg Al/kg)</td>
<td>31</td>
</tr>
<tr>
<td>Rabbit</td>
<td>a</td>
<td>chloride</td>
<td>subcutaneous</td>
<td>LD₁₀₀ 7,000 to 8,000 mg/kg (1011-1416 mg Al/kg)</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>a</td>
<td>sulfate</td>
<td>subcutaneous</td>
<td>LD₁₀₀ 7,000 to 8,000 mg/kg (552-630 mg Al/kg)</td>
<td>31</td>
</tr>
</tbody>
</table>

⁵Not specified.
⁶Whether anhydrous or octadecahydrate, not stated. Calculation of mg Al/kg based on anhydrous salt.
compound at the same dietary levels in beagle dogs (7 to 70 mg Al per kg per day) for 90 days showed similar concretions in the renal tubules in 3 of 8 animals (2 male, 1 female) at the highest dose level (38). Identical experiments (39, 40) were also performed by the same laboratory for the same producer with another aluminum compound, acidic sodium aluminum phosphate tetrahydrate, fed at dietary levels of 0.3, 1.0, and 3.0 percent in both rats (13 to 130 mg Al per kg per day) and beagle dogs (13 to 130 mg Al per kg per day) for 90 days. Microconcretions occurred in the renal tubules of female rats at all three dietary levels, but microconcretions were not observed in male rats or male or female dogs at any dietary level. In none of these studies (37-40) were significant abnormalities observed in weight gain, food consumption, and gross pathology, or in chemical tests on blood and urine.

In 1973 and 1974, Bio-Test Laboratories repeated the 90-day feeding tests on both basic and acidic sodium aluminum phosphate in female rats at lower dietary levels (0.03 to 0.1 percent) and found higher incidence of microconcretions in the kidney tubules of the treated as compared to the control animals (41, 42). In separate reports (43, 44) histologic evaluation of the kidney tissues from both rat and dogs fed the test compounds, led to the conclusion that: (a) the female rat is uniquely sensitive to the development of renal microconcretions; (b) spontaneous incidence of this lesion in the female rat can be increased by feeding inorganic phosphate; (c) the significance of this lesion is questionable because it is not associated with impaired renal function or other toxicologic manifestations. It is noteworthy that these reports (43, 44) indicate, contrary to a previous conclusion from the same laboratory (38), that neither male nor female dogs showed the presence of kidney microconcretions after feeding either basic or acidic sodium aluminum phosphate, even at dietary levels as high as 3 percent.

Essentially the same results were reported by Bio-Test Laboratories to another producer on their preparation of acidic sodium aluminum phosphate (45-48).

Finally, a series of studies with chicks demonstrated that aluminum sulfate (49) or aluminum hydroxide (50-52), incorporated in the feed of chicks for 3 to 5 weeks, caused progressive muscular weakness, rickets, and high mortality at the highest dietary levels. In two of these studies, where it was tried (49, 51), these effects were found to be reversed by administration of phosphate. Dosages at the beginning of feeding were in the range of 450 to 3,750 mg Al per kg per day.

Interpretation of the significance of some of these animal studies for man is difficult. However, studies in man have shed some additional light in this respect. Although the aluminum that is absorbed is readily excreted
by the normal human kidney, the elevated serum aluminum level that occurs in patients with chronic renal failure, particularly after ingestion of 35 mg Al per kg per day as aluminum hydroxide, suggests a possible toxic effect (53). It was noted that because the effects of hyperaluminemia are not fully known, the use of aluminum compounds in patients with advanced renal failure should be regarded with some concern. In these studies, modern analytical methods of neutron activation, atomic absorption spectrophotometry, and colorimetry were employed to determine aluminum. Because it is difficult to determine aluminum accurately in the plasma and urine by more commonly used methods, the authors regard much of the data obtained in routine biochemical laboratories as questionable. The concern about hyperaluminemia expressed by Berlyne et al. (53) has been challenged by Wrong and Swales (54) who regard the evidence as insufficient to warrant discontinuing the use of aluminum compounds in the treatment of hyperphosphatemia. A study in man has confirmed the possible deleterious interaction of aluminum salts in phosphorus metabolism, especially during long-term ingestion of aluminum containing antacids (21).

Recent work of Spencer et al. (55) bears on earlier studies where large amounts of antacids were reported to induce phosphorus depletion. They examined the effect of relatively small doses (16 to 51 mg Al per kg per day) of proprietary antacids on calcium and phosphorus metabolism in 11 patients. These studies showed an inhibition of intestinal absorption of phosphorus followed by an increase in calcium loss. The effect was attributed to the binding of dietary phosphorus in the intestine by aluminum. This effect was not seen when phosphorus-containing aluminum salts were used.

Long-term studies

Rats were raised for six generations on diets containing about 50 mg of Al per kg body weight as aluminum sodium sulfate for the first and second generations, and about 100 mg per kg for the succeeding generations, without untoward effects as estimated by rate of growth, maximum adult size, longevity, reproduction, and non-protein nitrogen determinations on blood samples (33). Microscopic examination of the kidneys of these rats failed to reveal any pathologic changes when compared with control rats.

A three-generation study with mice, revealed that doses of aluminum chloride in drinking water averaging 19.3 mg of Al per kg per day, produced no effect on reproduction and did not cause any histopathologic changes in the liver, spleen, or kidney in the first litter (13). No hematologic effects were detected. However, doubling the dose of aluminum reduced growth rate in second and third generation offspring.
Special studies

No teratogenicity was observed in the evaluation of orally administered aluminum sodium sulfate at levels up to 352 mg per kg in pregnant mice (day 6 through day 15 of gestation); up to 268 mg per kg in pregnant rats (day 6 through day 15 of gestation); up to 270 mg per kg in pregnant hamsters (day 6 through day 10 of gestation); up to 191 mg per kg in pregnant rabbits (day 6 through day 18 of gestation) (56). No defects were found in chick embryos injected with an aqueous solution of aluminum chloride into the yolk on the fourth day of incubation or onto the chorioallantoic membrane on the eighth day of incubation. The LD₅₀ was about 0.3 mg per kg (57). Aluminum sodium sulfate was considered nonteratogenic when tested by injection of an aqueous solution into the air cell or yolk of unincubated fertile eggs or after 96 hours of incubation. Doses ranged up to 1.0 mg per kg (58).

Mutagenic evaluation of three aluminum salts in a series of in vitro microbial assays have been reported (59-61). The assays included plate and suspension tests (both non-activated and activated with liver, lung or testicular homogenates from mice, rats, and monkeys) using Saccharomyces cerevisiae (strain D4) and Salmonella typhimurium (strains TA-1535, 1537, and 1538) as test organisms. Sodium aluminum sulfate (59) and aluminum ammonium sulfate (60) were found to exhibit no genetic activity in any of the tests. Acidic sodium aluminum phosphate (61) showed a marginal response in plate tests with Salmonella TA-1537 (unactivated) and with TA-1535 activated with rat liver homogenate. All other tests on acidic sodium aluminum phosphate were negative.

No evidence of carcinogenicity was found when an aluminum hydroxide suspension was given intraperitoneally daily to mice for 4 months at dosages up to about 200 mg Al per kg per day (62).

It is to be noted that the biological studies discussed in this section concern those aluminum compounds that are used as miscellaneous and/or general purpose food additives, namely, aluminum ammonium sulfate, aluminum potassium sulfate, aluminum sodium sulfate, aluminum sulfate, and sodium aluminum phosphate, and one compound, aluminum hydroxide, which is used in paper and paperboard food packaging materials. For the other aluminum compounds used in paper packaging materials, namely, aluminum oleate, aluminum palmitate, sodium aluminate, and sodium phosphaaluminate, no information is available on their biological properties or on the amounts that might migrate to foods, but all indications are that the amounts of aluminum that would be added to the diet from this source are extremely small.
Aluminum and its salts are found in varying amounts in nearly all foods. In addition to the aluminum occurring naturally in foods, man can be exposed to the aluminum added to foods, to that in aluminum antacids he may take, and to that from aluminum cooking vessels. It has been estimated that the daily aluminum intake for man from all dietary sources can range from 10 to 100 mg per day and that of this amount, the intake from aluminum compounds added to food may average about 20 mg per day, about 75 percent of which is in the form of sodium aluminum phosphate. In relation to body weight, these amounts are less than those needed to produce toxic responses in experimental animals. It should be noted, however, that this amount may be considerably increased by the consumption of aluminum-containing antacids.

When aluminum salts are ingested in excessive amounts, their toxicity appears to be associated with interference in phosphorus metabolism resulting in rachitic or osteomalacic effects, kidney damage, and interference with glucose metabolism, apparently due to interference with phosphorylating enzymes. These effects are reduced and controlled by maintaining sufficient phosphorus in the diet and are exacerbated by kidney dysfunction. Clearly, dietary phosphorus level is a controlling factor, and care should be taken by patients with kidney disease when consuming food containing high levels of aluminum salts. The high intake of phosphorus in the American diet may provide a protective effect, especially in persons who consume large amounts of aluminum antacid preparations that do not contain phosphorus. However, since high phosphate intakes cannot be assured for specific individuals at all times, and since there is some evidence that persons with kidney disease may be at risk, appropriate labeling or other means to indicate the possibility of such hazards may warrant consideration.

The Select Committee has found no relevant toxicologic studies on aluminum oleate, aluminum palmitate, sodium aluminate, and sodium phosphoaluminate (substances that may migrate to food from paper packaging materials). But the nature of the inorganic compounds at least does not suggest that, ingested in such small amounts, they would have a different effect than the other aluminum compounds considered in this report, all of which exhibit low orders of toxicity. Even in the absence of direct evidence, it cannot be concluded that the use of any of these compounds in packaging materials would have any likelihood of being hazardous.

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

1. There is no evidence in the available information on aluminum ammonium sulfate, aluminum potassium sulfate, aluminum sodium sulfate, aluminum
sulfate, acidic sodium aluminum phosphate, basic sodium aluminum phosphate, and aluminum hydroxide 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.

2. No consumption or biological information is available on aluminum oleate, aluminum palmitate, sodium aluminate, and sodium phosphoaluminate. However, there are no reasonable grounds to suspect a hazard to the public when they are consumed at the levels that are likely if these substances should migrate from paper and paperboard used as food packaging materials; or that might reasonably occur when they are used for this purpose in the future.
VI. REFERENCES CITED


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