EVALUATION OF THE HEALTH ASPECTS OF CERTAIN
CALCIUM SALTS 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. Jellef Carr, Ph.D., Director
Life Sciences Research Office
FASEB
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I. INTRODUCTION

This report concerns the health aspects of using certain calcium salts 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, announcement was made in the Federal Register of August 29, 1975 (40 FR 39917 and 39918) 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 certain calcium salts as food ingredients. The Select Committee received no requests for such a hearing on certain calcium salts.

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

*The document (PB-223 843/4) 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 certain calcium salts 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

Calcium acetate, calcium chloride, calcium gluconate and calcium phytate are GRAS substances under the provisions of the Code of Federal Regulations (2) as sequestrants [121.101(d)(6)]. In addition, calcium chloride and calcium gluconate are general purpose food additives [121.101(d)(8)], and calcium chloride is listed as a GRAS substance migrating to food from paper and paperboard products [121.101(h)] and cotton fabrics [121.101(i)] used in dry food packaging. These four calcium salts are evaluated in this report. Some data on calcium citrate, a sequestrant and general purpose food additive, are included for comparative purposes but calcium citrate is to be evaluated in a report on citric acid and citrates (3). Other forthcoming reports of the Select Committee will cover additional acetates (4), gluconates (5) and other calcium compounds (6).

Calcium has an important role in the nutrition of man and animals (7). Hormonal mechanisms control absorption of dietary calcium (including added calcium salts) allowing adaptation to a range of calcium intakes while maintaining a relatively constant blood calcium concentration of about 10 mg per 100 ml. Major functions of calcium include the formation and maintenance of bones and teeth, the physiology of muscle contraction, cell membrane integrity, the activity of several enzymes which have specific requirements for it, coagulation of the blood, and the regulation of the acid-base balance.

Sequestrants, or chelating agents, are used to stabilize foodstuffs by complexing metal ions that may otherwise catalyze or participate in undesirable reactions affecting color, flavor and texture. Acetic acid and gluconic acid (as 6-phosphogluconate) are metabolizable carbohydrates occurring
naturally in plants and animals. Phytic acid [1, 2, 3, 4, 5, 6-cyclohexane-
hexol phosphoric acid] does not occur in animal tissue but occurs in many
plant foodstuffs such as cereals, nuts, legumes, artichokes and potatoes (8).
The order in which metal ions are complexed by these sequestrants is:
acetate complexes $Co^{2+}>Zn^{2+}>Ni^{2+}>Ca^{2+}(9)$; citrate complexes $Fe^{3+}>Cu^{2+}$
$Ni^{2+}>Zn^{2+}>Co^{2+}>Ca^{2+}(9)$; gluconate complexes $Cu^{2+}>Zn^{2+}>Ca^{2+}(9)$; and
phytate complexes $Cu^{2+}>Zn^{2+}>Co^{2+}>Mn^{2+}>Fe^{3+}>Ca^{2+}(8)$.

No specifications have been found for food grade calcium phytate.
Specifications are given in the Food Chemicals Codex (10) for the other
calcium compounds evaluated in this report (Table I).

III. CONSUMER EXPOSURE DATA

A subcommittee of the National Research Council (NRC) surveyed
manufacturers in 1970 by questionnaire concerning the addition of GRAS
substances to foods and estimated the possible average daily intake of these
substances for various age groups (11). Based on information supplied by
those manufacturers who reported adding the substance to at least one food
in a category, weighted means were calculated for the usual and maximal
addition of the substance to foods in the category. 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 level of addition of certain
calcium salts are included in Table II. The Select Committee has no
information concerning changes in the level of addition of these calcium
salts to foods in recent years.

The NRC subcommittee estimated possible average daily intakes
(Table III) 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. Such an assumption is likely to lead to overestimates of
intake. The NRC subcommittee has recognized that in most cases its calcu-
lations of possible intakes are overstated, often by considerable margins.*

*An explanation for such overstatements is detailed in Section XI,
"Significance and Use of Data in Safety Evaluations," of the NRC subcom-
mittee's report (11). 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 I

Specifications for Calcium Salts (10)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Composition</th>
<th>Arsenic ppm</th>
<th>Heavy metals (as lead) ppm</th>
<th>Chloride ppm</th>
<th>Sulfate percent</th>
<th>Magnesium &amp; alkali salts percent</th>
<th>Loss on drying percent</th>
<th>Fluoride ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium acetate</td>
<td>(\geq 99.0) percent (\text{Ca(C}_2\text{H}_3\text{O}_2\text{)}_2), anhyd.</td>
<td>(\geq 3)</td>
<td>(\leq 25)</td>
<td>(\geq 500)</td>
<td>(\leq 0.1)</td>
<td>---</td>
<td>(\geq 7)</td>
<td>---</td>
</tr>
<tr>
<td>Calcium chloride</td>
<td>(\geq 99.0) percent and (\geq 107.0) percent (\text{CaCl}_2\cdot2\text{H}_2\text{O})</td>
<td>(\geq 3)</td>
<td>(\leq 20)</td>
<td>---</td>
<td>---</td>
<td>(\leq 1)</td>
<td>---</td>
<td>(\leq 40)</td>
</tr>
<tr>
<td>Calcium chloride anhydrous</td>
<td>(\geq 93.0) percent (\text{CaCl}_2)</td>
<td>(\geq 3)</td>
<td>(\leq 20)</td>
<td>---</td>
<td>---</td>
<td>(\leq 5)</td>
<td>---</td>
<td>(\leq 40)</td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td>(\geq 98.0) percent and (\geq 102.0) percent (\text{C}<em>{12}\text{H}</em>{22}\text{CaO}_{14}), after drying.</td>
<td>(\geq 3)</td>
<td>(\leq 20)</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>(\leq 3)</td>
<td>---</td>
</tr>
</tbody>
</table>

\(^1\)\(\geq\) = not less than
\(^2\)\(\leq\) = not more than
\(^3\)\(\leq 10\) ppm Pb
TABLE II

Level of Addition of Calcium Salts to Foods by Food Category (II)

<table>
<thead>
<tr>
<th>Food Category</th>
<th>Calcium acetate</th>
<th>Calcium chloride</th>
<th>Calcium citrate</th>
<th>Calcium gluconate</th>
<th>Calcium phytate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baked goods, baking mixes</td>
<td>0.07</td>
<td></td>
<td></td>
<td></td>
<td>1.59</td>
</tr>
<tr>
<td>Milk, milk products</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheese</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Processed fruits, juices, drinks</td>
<td>0.12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meat products</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fish products</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Processed vegetables, juices</td>
<td>0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condiments, relishes, salt substitutes</td>
<td></td>
<td>0.06</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Jams, jellies</td>
<td></td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweet sauces, toppings, syrups</td>
<td>0.01</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gelatins, puddings, fillings</td>
<td>0.19</td>
<td></td>
<td></td>
<td>0.03</td>
<td>2.34</td>
</tr>
<tr>
<td>Beverages Type I (nonalcoholic)</td>
<td>&lt;0.01</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beverages Type II (alcoholic)</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reconstituted vegetable proteins</td>
<td></td>
<td></td>
<td>1.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gravies, sauces</td>
<td></td>
<td></td>
<td>0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dairy products analogs</td>
<td></td>
<td></td>
<td>0.08</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>Sugar substitutes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Instant coffee and tea</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Baby formulas</td>
<td>0.01</td>
<td>0.10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Blanks in the table mean that the substance is not added to the foods indicated. Level of addition of calcium salts 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 Exhibit 50 of reference 11.
TABLE III

Possible Average Daily Intake of Added Calcium Salts by Age Group (mg) 

<table>
<thead>
<tr>
<th>Substance</th>
<th>0-5 months mg</th>
<th>0-5 months mg/kg</th>
<th>6-11 months mg</th>
<th>6-11 months mg/kg</th>
<th>12-23 months mg</th>
<th>12-23 months mg/kg</th>
<th>2-65+ years mg</th>
<th>2-65+ years mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium acetate</td>
<td>4</td>
<td>1</td>
<td>25</td>
<td>3</td>
<td>27</td>
<td>2</td>
<td>40</td>
<td>1</td>
</tr>
<tr>
<td>Calcium chloride</td>
<td>52</td>
<td>10</td>
<td>121</td>
<td>15</td>
<td>212</td>
<td>19</td>
<td>345</td>
<td>6</td>
</tr>
<tr>
<td>Calcium citrate</td>
<td>329</td>
<td>66</td>
<td>71</td>
<td>9</td>
<td>26</td>
<td>2</td>
<td>6</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td>101</td>
<td>20</td>
<td>710</td>
<td>89</td>
<td>1194</td>
<td>109</td>
<td>2665</td>
<td>44</td>
</tr>
<tr>
<td>Calcium phytate</td>
<td>***¹</td>
<td>***¹</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

possible usual daily intake of calcium salts by age group was estimated from the data in Table II and other factors as explained in the exhibits cited in the footnote to Table II. Calculated intake, mg/kg body weight, was based on an average weight of 60 kg for an adult (12) 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 (13).

¹ Asterisks (***¹) in the table mean that there were insufficient data on which to base an estimate.
Because of factors detailed in Section XI of the subcommittee's report (11) they stated that the possible 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. The Select Committee believes the average intakes (Table III) calculated by the NRC subcommittee could be achieved only by a small fraction of the population.

In the use of calcium salts in foods, manufacturing practices appear to vary widely from one manufacturer to another and, within a company, from product to product. Thus, it is not surprising that the weighted mean of the usual concentration of a calcium salt in a food category, as reported in Table II, is unsuitable for estimating average or 50th percentile intakes. Average daily intakes of calcium salts are likely to be of the order of per capita daily intakes calculated from the quantities used annually in foods (Table IV) because no more could be ingested than is used.

Most manufacturers apparently do not add calcium acetate or calcium gluconate to baked goods and baking mixes or to gelatins, puddings and fillings — fewer than three NRC survey respondents reported these uses (11). The extremely high values listed in Table II for usual addition of calcium gluconate to the food category — baked goods, baking mixes — and the relatively high values listed for usual addition of calcium acetate and calcium gluconate to the food category — gelatins, puddings, fillings — presumably pertain to only one or a few products. At least in the case of calcium gluconate, it seems likely that the precentage listed for usual addition actually applied to a dry powder rather than to the food as consumed. It is presumably because of these few high values for usual additions that the intakes of individuals over 2 years old have been estimated in Table III to be 40 mg per day for calcium acetate and 2,665 mg per day for calcium gluconate. Per capita intakes calculated from quantities used annually (Table IV) are 1 mg per day for calcium acetate and 3 mg per day for calcium gluconate. The overestimation of intakes of calcium acetate and calcium gluconate appears to apply to younger individuals as well as to those over 2 years old.

In the case of calcium chloride, the estimated intake for individuals over 2 years old is given as 345 mg per day in Table III. The intake based on the quantity of calcium chloride used annually (Table IV) is 160 mg per day. The Select Committee believes that the intakes in Table III are overestimated for individuals more than 2 years old primarily because of high values for usual additions in Table II with respect to three food categories: baked goods, baking mixes; processed fruits, juices, drinks; and processed vegetables, juices. For individuals less than 2 years old, the assumption that calcium chloride is added at a level of 0.01 percent to all
<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>Calcium acetate</td>
<td>1.0</td>
<td>40,000</td>
<td>1</td>
</tr>
<tr>
<td>Calcium chloride</td>
<td>3.7</td>
<td>12,000,000</td>
<td>160</td>
</tr>
<tr>
<td>Calcium citrate</td>
<td>4.0</td>
<td>14,000</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td>6.1</td>
<td>240,000</td>
<td>3</td>
</tr>
<tr>
<td>Calcium phytate</td>
<td>8.4</td>
<td>2,600</td>
<td>&lt;1</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 (II).

\(^2\) 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 205 million.
foods of the food categories milk products and formula products, contributes further to the overestimation of intake in Table III. Fewer than three NRC respondents reported adding calcium chloride to any food in either of these categories (11).

Calcium phytate is apparently not widely added to foods. It was reported used in one food category by fewer than three NRC respondents. The quantity used in 1970, 2,600 kg, supports this conclusion (11).

The Select Committee is well aware that there are other dietary sources of calcium and suggests that additional sources will need to be considered if the biological impact of total dietary intake of calcium should become a matter of concern.

The Joint FAO/WHO Expert Committee on Food Additives, in its reports on calcium acetate and calcium chloride (14), has concluded that "the average daily intake of this element [calcium] for man may safely extend from about 400 mg up to 2 or even 3 g. The latitude for dietary variation without ill-effects due to calcium is therefore wide. The contribution of calcium derived from compounds used as food additives according to present practice is unlikely to alter substantially the total intake. For this reason, no specific figure has been proposed as an acceptable daily intake for calcium acetate or calcium chloride."

IV. BIOLOGICAL STUDIES

Absorption, metabolism, and excretion

The absorption, metabolism, and excretion of calcium consumed as salts and the interrelationships of calcium, phosphorus, and vitamin D are reviewed and described in detail by Hegsted (7). The Select Committee will discuss these interrelationships in a forthcoming report on phosphates (15) because the calcium salts commonly used as nutrients and for dietary supplements are generally phosphates.

Evidence for the metabolism of acetate (4) and gluconate (5) will be discussed in other reports of the Select Committee. After reviewing available literature on phytic acid, Oberleas (8) has concluded that the phosphate of phytic acid should be considered as unavailable and also that zinc may not be utilisable when complexed by phytic acid at the pH of the small intestine of animals. Reinhold et al. (16) observed negative zinc and calcium balances in three human subjects fed diets rich in phytic acid (35 to 46 mg per kg body weight).
Acute toxicity

The oral LD$_{50}$ of calcium acetate has been reported to be 4.28 g per kg in the rat (17). Prioreschi and Selye (18) reported that 6 of 10 forcibly restrained female rats (90 to 100 g body weight) died within 24 hours after an initial dose of 2 millimoles of calcium acetate in 3 ml water by gavage followed by a similar dose 8 hours later (total dose 6.3 g per kg). No deaths occurred when unrestrained rats were dosed similarly. One of ten rats died following a single dose of 4 millimoles in 3 ml water by gavage. Calcifying cardiovascular lesions were described only in animals of the groups in which deaths occurred.

The oral LD$_{50}$ of calcium chloride in the rat is approximately 5 g per kg and in the rabbit 1.38 g per kg (19). Mahorner (20) found the lethal oral dose to be above 2 g per kg for the dog. For man, the oral lethal dose is estimated as 30 g (21). Hall (22) has called attention to the use of calcium chloride (6 to 8 g per day) for infants afflicted with neonatal tetany. While corrosive effects of this substance were reported in these cases, lethality cannot be ascribed to use of calcium chloride even with these very high doses. However, Durlacher et al. (23) reported that two infants died following the use of calcium chloride for treatment of tetany. One weighing 2,900 g was given 4 g of the substance by gavage, and the other weighing 3,060 g was given 3 g, followed by 1 g at each four-hour feeding thereafter. The authors concluded that the recommended dose of this substance, ranging from 2 to 4 g, was dangerous for the newborn infant.

After intramuscular injection of calcium chloride in rats, Boyd and Seymour (24) found that the LD$_{50}$ was about 25 mg per kg. However, no toxic reactions were observed when this substance was administered orally in doses up to 1 g per kg indicating that calcium chloride given by gastric intubation is not absorbed well from the gastrointestinal tract.

The intravenous LD$_{50}$ for calcium gluconate has been reported by Coulston et al. (25) to be about 1 g per kg in the mouse.

Short-term studies

Sharpless et al. (26) studied a possible relationship between thyroid enlargement in rats and the administration of calcium salts. Calcium chloride was administered as 1 percent in the drinking water (about 1 g per kg body weight) or 2 percent in a goitrogenic basal diet (about 2 g per kg body weight) over a period of 12 weeks. Calcium chloride caused no thyroid enlargement when compared to that produced by the basal diet except for a slight effect when vitamin D was present. No microscopic alterations were observed.
In a study conducted by Smith (27), calcium gluconate and calcium chloride were administered by gavage to two groups of ten 200 g rats to give approximately 0.4 g of calcium per kg body weight per day (the gluconate as a suspension and the chloride in water solution). Five of the animals receiving calcium chloride for 65 days and two receiving calcium gluconate for 70 days died prior to sacrifice. Microscopic examination was made of the heart, kidney and liver from animals given the gluconate and no histological alterations were observed. Similarly, no microscopic abnormalities were observed in the animals given calcium chloride. The author concluded that calcium chloride was more toxic than calcium gluconate when given orally.

Acidosis can be produced in rabbits given 1.5 to 2.5 g per kg of calcium chloride (28). Twenty percent calcium chloride solutions (0.75 to 1.5 g per kg body weight) can produce severe gastric damage consisting of mucosal necrosis and ulceration in rabbits (23). In one instance, the stomach was perforated, but the intestine was free of lesions 48 hours after administration of the dose. Oral administration of the same dosage of calcium chloride in more dilute solutions, ranging from 5 to 15 percent, failed to produce lesions in older rabbits but severe ulcers appeared in unweaned young rabbits. Therefore, it appears that the toxic effect is caused by the concentration of calcium chloride in the solution rather than by the amount of calcium given.

Calcium from [\textsuperscript{46}Ca]\textsuperscript{calcium phytate}, 0.3 percent supplement, was absorbed and deposited in the femurs of five rats given the diet for 3 days (29). All rats remained healthy.

No short-term studies on calcium acetate have come to the attention of the Select Committee. No reports of long-term studies have come to the attention of the Select Committee on any of the calcium salts.

**Special studies**

Lieberman (30), studying the therapeutic use of calcium gluconate as a calcium source for man, administered 10 g of this salt orally to ten fasting individuals and to an additional ten after a standard breakfast. The salt produced a definite diarrheal tendency in the subjects with empty stomachs but no untoward effects were reported for the group receiving the salt after a meal.

No studies designed to test the carcinogenicity or mutagenicity of calcium acetate, chloride, gluconate or phytate have been found by the Select Committee.
Teratologic studies of calcium chloride in mice, rats, and rabbits have been reported (31). Oral administration of up to 189 mg per kg in mice (day 6 through 15 of gestation), up to 176 mg per kg in rats (day 6 through 15 of gestation), and up to 169 mg per kg in rabbits (day 6 through 18), 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.

Calcium chloride and calcium gluconate at levels up to 50 mg per kg of egg are reported to have no teratogenicity for the developing chick embryo; calcium gluconate exhibited only moderate embryo toxicity (32). These findings are not considered significant.

V. OPINION

Extensive studies have been made to determine the nutritional significance of calcium and its salts. Calcium and the acetate, chloride, and gluconate anions are common constituents of food and are metabolized by the normal metabolic processes in man. Phytic acid is a naturally occurring constituent of foodstuffs of plant origin. The very limited use of calcium phytate appears insignificant in light of the natural occurrence of phytic acid. A review of the concentrations of calcium compounds normally present in or added to foods provides no evidence that suggests possible untoward effects at these levels.

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

There is no evidence in the available information on calcium acetate, calcium chloride, calcium gluconate, and calcium phytate 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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