EVALUATION OF THE HEALTH ASPECTS OF MAGNESIUM SALTS AS FOOD INGREDIENTS

1976

Prepared for

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

Contract No. FDA 223-75-2004
EVALUATION OF THE HEALTH ASPECTS OF MAGNESIUM SALTS

AS FOOD INGREDIENTS

1976

Prepared for

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

Contract No. FDA 223-75-2004

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. Jeffff Carr, Ph.D., Director
Life Sciences Research Office
FASEB
<table>
<thead>
<tr>
<th>CONTENTS</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>9</td>
</tr>
<tr>
<td>V. Opinion</td>
<td>15</td>
</tr>
<tr>
<td>VI. References cited</td>
<td>17</td>
</tr>
<tr>
<td>VII. Scientists contributing to this report</td>
<td>23</td>
</tr>
</tbody>
</table>
I. INTRODUCTION

This report concerns the health aspects of using magnesium 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, an announcement was made in the Federal Register of January 7, 1977 (42 FR 1519 to 1521) 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 magnesium salts as food ingredients. The Select Committee received no requests for such a hearing on magnesium salts.

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, 1976, 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 document (PB 228 550/0) is available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.
The Select Committee on GRAS Substances of LSRO is making its evaluations of these substances in full recognition of the foregoing provisions. In reaching its conclusions on safety, the Select Committee, in accordance with FDA's guidelines, is relying primarily on the absence of substantive evidence of, or reasonable grounds to suspect, a significant risk to the public health. While the Select Committee realizes that a conclusion based on such reasoned judgment is expected even in instances where the available information is qualitatively or quantitatively limited, it recognizes that there can be instances where, in the judgment of the Select Committee, there are insufficient data upon which to base a conclusion. The Select Committee, 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 magnesium 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

Magnesium carbonate, hydroxide, and oxide are GRAS substances under the provisions of the Code of Federal Regulations (2) as miscellaneous and/or general purpose food additives [21 CFR 121.101(d)(8)]. Magnesium stearate also is classified as GRAS but with the limitation: "as migratory substance from packaging materials when used as stabilizer." In addition, magnesium stearate is included among regulated additives that are permitted for use as binders, emulsifiers, and anticaking agents in food in accordance with good manufacturing practice (21 CFR 121.1071). The stearic acid from which magnesium stearate is made must conform to 21 CFR 121.1070 and must contain no chick-edema factor and not over 2 percent unsaponifiable matter.

Magnesium oxide, sulfate, dibasic phosphate and tribasic phosphate are generally recognized as safe as nutrients and/or dietary supplements [21 CFR 121.101(d)(5)]. Magnesium chloride has unpublished FDA approval as a food ingredient (3). In addition, magnesium carbonate, chloride, hydroxide and sulfate are listed as GRAS substances migrating to food from paper and paperboard products used in food packaging [21 CFR 121.101(h)] and magnesium silicate is listed as a GRAS anticaking agent [21 CFR 121.101(d)(1)]. Magnesium gluconate is included on a partial listing of substances
presumed to be GRAS by FDA but not published (4). Magnesium silicate
and gluconate will not be evaluated in this report but will be considered in
reports of the Select Committee on silicates and gluconates, respectively.

As general purpose food additives, magnesium carbonate, hydroxide
and oxide are used as alkalis in adjusting the acidity of foods. The carbonate,
hydroxide and chloride are employed as color-retention agents. In addition
to the foregoing, magnesium carbonate, the most widely used magnesium
salt, serves as a drying agent, bleach ingredient, anticaking agent and
carrier for other additives (5). Other uses of magnesium salts reported
in a survey of the food industry by a National Research Council (NRC) sub-
committee were as firming agents, lubricants, flavor enhancers, and pro-
cessing aids (6). Pharmaceutically, the hydroxide, oxide, and carbonate are
used as antacids (7) and the hydroxide (milk of magnesia) and sulfate (Epsom
salt) as laxatives (8).

Magnesium is an essential nutrient for plants and animals and is a
natural constituent of fruits, vegetables, grains, meats and seafoods (9,10).
It is the fourth most abundant cation in the human body and the second most
plentiful intracellularly. The average 60-kg human adult body contains
about 24 g of magnesium of which about one-half resides in bone. Although
plasma levels vary between 1.7 and 3.0 mg per dl, very little is contained in
extracellular fluid (11). Magnesium is essential for the production and
transfer of energy, for protein, fat, and nucleic acid synthesis, for con-
tractility in muscle and excitability in nerve, and for the activity of numer-
ous enzyme systems (11-13). The daily dietary allowances (RDA's) recom-
mended by the Food and Nutrition Board, National Academy of Sciences-
National Research Council range from 60 mg for infants up to 450 mg for
pregnant and lactating women (14).

Specifications are given in the Food Chemicals Codex (15) for the
magnesium compounds evaluated in this report (Table I).

III. CONSUMER EXPOSURE DATA

An NRC subcommittee surveyed food processors by questionnaire
concerning the level of addition of GRAS substances to foods in 1970 and
estimated the possible average daily intake of these substances for various
age groups (6). Based on information supplied by those processors who re-
ported adding a GRAS 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. Weighted means of the usual level of addition of
certain magnesium salts are given in Table II. No uses were reported for
tribasic magnesium phosphate. Data on the usage of magnesium chloride
were not requested but were volunteered by three or fewer respondents. It
**TABLE I**

**Specifications for Magnesium Salts (15)**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Composition</th>
<th>Arsenic ppm</th>
<th>Heavy metals (as lead) ppm</th>
<th>Lead ppm</th>
<th>Calcium oxide, %</th>
<th>Other ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium carbonate</td>
<td>≦40.0% and ≦43.5% MgO</td>
<td>≦3</td>
<td>≦30</td>
<td>≦10</td>
<td>≦0.6</td>
<td>---</td>
</tr>
<tr>
<td>Magnesium chloride</td>
<td>≦99.0% and ≦105.0% MgCl₂·6H₂O</td>
<td>≦3</td>
<td>≦10</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>≦200 ppm sulfate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium hydroxide</td>
<td>≦95.0% Mg(OH)₂ after drying</td>
<td>≦3</td>
<td>≦40</td>
<td>≦10</td>
<td>≦1.0</td>
<td>---</td>
</tr>
<tr>
<td>Magnesium oxide</td>
<td>≦96.0% MgO after ignition</td>
<td>≦3</td>
<td>≦40</td>
<td>≦10</td>
<td>≦1.5</td>
<td>---</td>
</tr>
<tr>
<td>Magnesium phosphate,</td>
<td>≦96.0% Mg₃P₂O₇ after ignition</td>
<td>≦3</td>
<td>≦30</td>
<td>≦5</td>
<td>---</td>
<td>Fluoride ≦10</td>
</tr>
<tr>
<td>dibasic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium phosphate,</td>
<td>≦98.0% and ≦101.5% Mg₃(PO₄)₂ after</td>
<td>≦3</td>
<td>≦30</td>
<td>≦5</td>
<td>---</td>
<td>Fluoride ≦10</td>
</tr>
<tr>
<td>tribasic</td>
<td>ignition</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium stearate*</td>
<td>≦6.8% and ≦8.0% MgO equivalent</td>
<td>≦3</td>
<td>≦40</td>
<td>≦10</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>≦99.5% MgSO₄ after ignition</td>
<td>≦3</td>
<td>---</td>
<td>≦10</td>
<td>---</td>
<td>Selenium ≦30</td>
</tr>
</tbody>
</table>

*Conforms to FDA specifications for salts of fatty acids and fatty acids derived from edible fat sources.*
### TABLE II

**Level of Addition of Magnesium Salts to Foods by Food Category** *(5)*

*(Weighted mean percent)*

<table>
<thead>
<tr>
<th>Food category</th>
<th>Carbonate</th>
<th>Hydroxide</th>
<th>Oxide</th>
<th>Dibasic phosphate</th>
<th>Stearate</th>
<th>Sulfate</th>
<th>Chloride**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baked goods, baking mixes</td>
<td>0.23</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grain products such as pasta or rice dishes</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milk, milk products, miscellaneous products</td>
<td>0.07</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheese</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frozen dairy desserts, mixes</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meat products</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poultry products</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fish products</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Processed vegetables, juices</td>
<td>***</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condiments, relishes, salt substitutes</td>
<td></td>
<td>0.03</td>
<td>0.67</td>
<td></td>
<td>&lt;0.01</td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>Soft candy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sugar, confections</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td>0.02</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Soups, soup mixes</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snack foods</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beverages, nonalcoholic</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Gravies, sauces</td>
<td>0.02</td>
<td></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>0.01</td>
<td></td>
<td>***</td>
</tr>
<tr>
<td>Hard candy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chewing gum</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seasonings and flavors</td>
<td>0.91</td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
<td>0.33</td>
<td>1.00</td>
</tr>
<tr>
<td>Baby formulas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
</tbody>
</table>

* Blanks in the table mean that the substance is not added to the foods indicated. Level of addition of magnesium 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 Section X and Exhibit 50 of reference 6.

**Data on usage of magnesium chloride was not requested in the NRC survey but was volunteered by some respondents.**

***Insufficient data on which to base an estimate.
is to be noted that the weighted means do not express the highest percentage of a salt added by any food processor; they do not indicate the specific foods in a category which contain the magnesium salt and many foods in these categories do not contain added magnesium salts; moreover, they do not necessarily represent the levels used by any one food processor in its products in the food categories listed.

The NRC subcommittee estimated possible average daily intakes of magnesium salts added to foods (Table III) from Market Research Corporation of America (MRCA) data on the mean frequency of eating food 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 contained 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 intake are overstated, often by considerable margins. That this is the case for magnesium salts is indicated by comparison of the per capita daily intake of a salt calculated from the poundage used in foods (Table IV) with the intake estimated for the 0 to 5 month age group from the level of addition of the salt to foods (Table III). Intake values in Table III exceed those in Table IV by factors of 15 to 125.

Magnesium carbonate added to baked goods and baking mixes was the largest contributor to the estimated intake of magnesium salts by the 2 to 65+ year age group (6). However, no more than three companies reported this use for magnesium carbonate. Moreover, this salt is not permitted as an ingredient in wheat flour, bread or rolls by FDA identity standards for these products except in combination with benzoyl peroxide as an optional bleaching agent for flour (18), and it appears that magnesium carbonate is used only in a few specialty baked products.

The estimated daily intakes of dibasic magnesium phosphate (6) for the 0 to 5 month (1107 mg) and the 6 to 11 month (226 mg) age groups appear to be greatly overestimated. Infant formulas were the only infant food to which this salt was reported to be added. The weighted mean level of addition, 0.33 percent, (Table II) appears to be in error. Of the two most widely used non-milk based infant formulas (19) to which a magnesium salt is added as a nutrient supplement, one contains 0.016 percent magnesium chloride and the other 0.05 percent dibasic magnesium phosphate, both expressed on the ready-to-use basis (20). Less than 10 percent of infants receive non-milk based formulas (19).

*An explanation for such overstatements is detailed in Section XI, "Significance and Use of Data in Safety Evaluations," of the NRC subcommittee's report (6).
### TABLE III

Possible Average Daily Intake of Added Magnesium Salts by Age Groups\(^a\)\(^{\text{(6)}}\)

<table>
<thead>
<tr>
<th>Substance</th>
<th>0-5 mo (\text{mg})</th>
<th>0-5 mo (\text{mg/kg})</th>
<th>6-11 mo (\text{mg})</th>
<th>6-11 mo (\text{mg/kg})</th>
<th>12-23 mo (\text{mg})</th>
<th>12-23 mo (\text{mg/kg})</th>
<th>2-65+ yrs (\text{mg})</th>
<th>2-65+ yrs (\text{mg/kg})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium carbonate</td>
<td>8</td>
<td>1</td>
<td>63</td>
<td>8</td>
<td>134</td>
<td>12</td>
<td>334</td>
<td>6</td>
</tr>
<tr>
<td>Magnesium hydroxide</td>
<td>4</td>
<td>1</td>
<td>45</td>
<td>6</td>
<td>39</td>
<td>4</td>
<td>28</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Magnesium oxide</td>
<td>30</td>
<td>6</td>
<td>8</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Magnesium phosphate, dibasic</td>
<td>1107(^b)</td>
<td>221(^b)</td>
<td>226(^b)</td>
<td>28(^b)</td>
<td>74</td>
<td>9</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1</td>
<td>&lt;1</td>
<td>15</td>
<td>2</td>
<td>25</td>
<td>3</td>
<td>41</td>
<td>1</td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>3</td>
<td>&lt;1</td>
<td>6</td>
<td>1</td>
<td>12</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

\(^a\) Calculated intake, \(\text{mg per kg body weight}\), was based on an average weight of 60 kg for an adult (16) 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 (17).

\(^b\) Greatly overestimated. See text for discussion.
### TABLE IV

**Consumption of Magnesium Salts Based on Estimated Total Quantities of Magnesium Salts Used Annually in Foods (6)**

<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>Intake calculated from quantity used&lt;sup&gt;c&lt;/sup&gt; mg/person/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium carbonate</td>
<td>1.9</td>
<td>377,000</td>
<td>5.1</td>
</tr>
<tr>
<td>Magnesium hydroxide</td>
<td>---</td>
<td>129,000</td>
<td>1.7</td>
</tr>
<tr>
<td>Magnesium oxide</td>
<td>43</td>
<td>3,300</td>
<td>0.04</td>
</tr>
<tr>
<td>Magnesium phosphate, dibasic</td>
<td>2.9</td>
<td>9,700</td>
<td>0.13</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>13</td>
<td>177,000</td>
<td>2.4</td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>1.1</td>
<td>11,500</td>
<td>0.15</td>
</tr>
</tbody>
</table>

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

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

<sup>c</sup> Based on the total used in 1970 and a U.S. population of 205 million.
The Select Committee considers the poundage data in Table IV to be more reliable than the estimated possible daily intakes in Table III as a basis for estimating the contribution of GRAS magnesium salts to the dietary intake of magnesium. On the basis of these data the per capita daily usage of magnesium from the addition of these salts to foods is 2.5 mg.

Drinking water normally contributes to the magnesium intake. The median hardness (as CaCO₃) of finished municipal water supplies of the 100 largest cities of the United States is 90 ppm with 26 ppm calcium and 6.25 ppm magnesium (21). Maximal values were 738, 145, and 120 ppm, respectively. The softest waters contained no calcium or magnesium. Assuming a water intake of 1 liter per day (22), the daily intake of magnesium at median hardness would be 6.25 mg and 120 mg at maximal hardness.

Seelig (23) in 1964 estimated that the average American diet provided about 300 mg of magnesium daily. She recommended a magnesium intake of 7 to 10 mg per kg of body weight and concluded that some diets furnished inadequate amounts. Schroeder et al. (10), on the basis of an extensive analysis of common food items, concluded that the American diet may provide less than 6 mg per kg of body weight. A 1965 U.S. Department of Agriculture nationwide survey of food intake of individuals (24) indicated that the magnesium intake of several sex-age groups was below the NRC Food and Nutrition Board's RDA for magnesium (14). In 1974, the Food and Nutrition Board recommended that cereal grain products be fortified with magnesium in view of evidence of potential risk of deficiency among significant segments of the population (25).

The Joint FAO/WHO Expert Committee on Food Additives placed no restrictions, except for good manufacturing practice, on the food additive use of magnesium hydroxide, oxide, carbonate (26), and stearate (27), provided that the contribution made to the dietary load of magnesium is considered acceptable. The Codex Alimentarius Commission has approved a maximum level of 10 g per kg of product for magnesium oxide and tribasic magnesium phosphate as anticaking agents in milk and cream powders, and a maximum level of 15 g per kg for magnesium carbonate and magnesium stearate as anticaking agents in powdered sugar or dextrose (28).

IV. BIOLOGICAL STUDIES

Absorption, metabolism, excretion

Graham et al. (29) measured plasma radioactivity at various intervals after oral administration of [²⁵Mg] magnesium chloride to 13 adult humans on diets containing normal (240 mg per day or about 4 mg per kg of body weight), low (23 mg per day or about 0.4 mg per kg) and high (560 mg per
day or about 9 mg per kg) levels of magnesium. The high level diet was prepared by supplementation of the normal diet with magnesium acetate. Appreciable radioactivity was present in the plasma at one hour; it rose rapidly to a maximum at 3.5 to 6 hours, then fell slowly to about half the maximum value at 24 hours. Total absorption was 75.8, 44.3 and 23.7 percent on the low, normal and high magnesium diets, respectively. Rate of absorption was constant after 2 to 3 hours and continued more or less constant for the next four to six hours by which time about 80 percent of the total absorption had occurred. This period is the time taken for a meal to traverse the small intestine and suggests that absorption occurs from the small intestine. However, absorption from the colon also may occur as demonstrated by Stevens and Wolff (30) who found a significant increase in serum magnesium levels after giving hypertonic solutions of magnesium sulfate by enema to 6 male adults.

Aikawa et al. (31) explored the kinetics of distribution of magnesium-28 (salt not specified) in 9 normal individuals and 16 patients with various diseases. In the normal subjects a mean of 19.8 percent of the radioactivity appeared in the urine within 24 hours after intravenous administration of 144 to 360 mg (2.5 to 6 mg per kg) of stable magnesium. Fecal excretion was negligible which was taken to mean that most of the magnesium in the stool was of exogenous origin. Exchange of the isotope with the stable ion in bone, muscle and erythrocytes was very slow. There were no marked differences between the results obtained from the healthy subjects and those suffering from diabetes mellitus and hepatic diseases.

Consolazio et al. (32) studied the excretion of magnesium in human sweat and concluded that under extreme conditions of perspiration (100°F and 70 percent relative humidity environment) 25 percent of the daily magnesium loss could be attributed to sweat loss.

Seelig (23, 33) concluded from a review of balance studies that both men and women on low calcium intakes (under 10 mg per kg per day) were in negative calcium balance when the magnesium intake was below 5 mg per kg per day. At higher magnesium intakes, up to 10 mg per kg per day, calcium retention was improved but above this magnesium level calcium balances were again negative. At moderate to high calcium intakes (over 10 mg per kg per day) there was calcium retention by men but very little by women when
the magnesium intake was below 7 mg per kg per day; above this magnesium intake, calcium retention increased for both sexes.

Increased absorption of magnesium by 90- to 110-g rats fed calcium-deficient diets, as evidenced by decreased fecal elimination and increased urinary excretion of magnesium, was reported by Alcock and MacIntyre (34). No significant increase was noted in plasma magnesium concentration. In rats fed magnesium-deficient diets and showing signs of magnesium deficiency, plasma calcium levels increased and were associated with increased absorption of calcium from the gut. Total calcium absorbed was about equal to the net calcium plus magnesium absorbed by normal control animals. The authors suggested that these results indicated a common transport mechanism for calcium and magnesium in both the intestine and the renal tubule.

Clark (35) investigated the effects of supplemental magnesium chloride on calcium and phosphorus metabolism in adult male rats fed semisynthetic diets containing 0.2 to 0.8 percent phosphorus and 0.2 to 1.6 percent calcium in various combinations. The basal diet contained 0.05 percent magnesium and control animals received approximately 50 mg (15 mg per kg body weight per day) of magnesium during a 12-day balance period while the magnesium-supplemented rats received 800 to 1000 mg (about 250 mg per kg per day). Supplemental dietary magnesium increased calcium absorption and calcium balance was more positive when the diet contained at least 0.4 percent calcium; urinary calcium was increased at all calcium levels in response to supplemental magnesium. Provided the diet contained at least 0.4 percent phosphorus, supplemental magnesium made the phosphorus balance more positive; urinary phosphorus was decreased and phosphorus absorption was increased irrespective of calcium level. The apparent contradiction to the foregoing results of Alcock and MacIntyre (34) who found that calcium absorption was increased at very low levels of dietary magnesium, was attributed by Clark to the fact that Alcock and MacIntyre used young rats that exhibited signs of magnesium deficiency whereas he studied adult rats on magnesium adequate diets.

Massry et al. (36) evaluated the renal handling of magnesium in female dogs infused with magnesium chloride or magnesium sulfate, and given 1.0 to 3.0 µg magnesium per minute per kg body weight over 3 to 6 hours. The results indicated that magnesium excretion is determined by filtration and reabsorption without evidence for tubular secretion. The proportion of filtered magnesium excreted during magnesium sulfate infusion was not different from that observed with magnesium chloride infusion for any given level of diffusible serum magnesium. Parathyroid extract administration during magnesium infusion caused a decrease in the percent of filtered magnesium excreted and appeared to enhance magnesium reabsorption.
Smith et al. (37) investigated the distribution of magnesium ion in adult female dogs following intravenous or intraperitoneal administration of magnesium sulfate (31 to 42 mg Mg per kg of body weight). During the first three or four hours after injection the magnesium ions were distributed throughout the extracellular fluid. Subsequently, however, 11 to 54 percent of the injected magnesium was segregated from the extracellular fluid to elsewhere in the body. About 70 percent of the intravenous and 50 percent of the intraperitoneal dose were recovered in the urine within 24 hours. Only about 9 percent of the intraperitoneal dose was recovered in the feces during this time.

Absorption of magnesium from magnesium oxide, lactate and gluconate and its effect on the metabolism of calcium were investigated by Barbour and Winter (38) who gave dogs that had been kept on a diet adequate in calcium, magnesium, and phosphorus, doses of 50 to 200 mg of these salts per kg body weight by stomach tube. At the highest dosage an increase in serum magnesium resulted which was the same for all three salts despite the fact that gluconate contains only one-twelfth as much magnesium, and lactate one-seventh as much magnesium, as an equal weight of magnesium oxide. Retention of calcium in dogs fed high levels of magnesium gluconate for 19 to 34 days was dependent upon calcium and phosphorus intake.

**Acute toxicity**

The LD$_{50}$ for subcutaneously injected magnesium chloride in white mice was about 270 mg magnesium per kg of body weight (39) and was 14 mg magnesium per kg when administered intravenously (40). The intraperitoneal LD$_{50}$ dose in 100 g Wistar rats was dependent on the concentration of magnesium in the solution injected and also on the anion as shown in Table V. In adult rabbits, the LD$_{50}$ dose for subcutaneously administered magnesium chloride was 185 mg magnesium per kg of body weight (42)

**TABLE V**

<table>
<thead>
<tr>
<th>Concentration, mg Mg/ml:</th>
<th>6.5</th>
<th>13.0</th>
<th>17.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium chloride</td>
<td>100</td>
<td>90</td>
<td>66</td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>150</td>
<td>130</td>
<td>140</td>
</tr>
<tr>
<td>Magnesium acetate</td>
<td>100</td>
<td>100</td>
<td>73</td>
</tr>
<tr>
<td>Magnesium adipate</td>
<td>200</td>
<td>180</td>
<td>160</td>
</tr>
</tbody>
</table>
No information was available to the Select Committee on animal studies of the acute toxicity of magnesium carbonate, hydroxide, oxide, dibasic phosphate, tribasic phosphate or stearate.

Magnesium sulfate has caused acute toxicity, including fatalities, in humans who ingested large doses either accidentally or as an oral laxative (43-45); death resulted when a 160-g dose was given accidentally by duodenal tube to a patient (46).

Signs of magnesium sulfate toxicity are, in general, the same for all species, i.e., convulsive seizures followed by narcosis and at sufficiently high levels, death (47). When large amounts of the salt are administered either orally or rectally, the kidneys may not remove magnesium from the bloodstream fast enough to prevent accumulation of concentrations toxic to the central nervous system (30). From studies on nephritic patients it was concluded that 20 to 30 g of magnesium sulfate (330 to 500 mg per kg) used as a laxative can induce magnesium coma that could be mistaken for uremic coma (48). This dosage produced an increase in plasma magnesium of about 7 to 9 mg per dl whereas in normal individuals it produced a maximum increase of 0.4 mg per dl.

**Short-term studies**

In studying the rearing of guinea pigs on semisynthetic diets containing casein, sucrose, soybean oil, cellulour or gum arabic for bulk, and vitamin and mineral supplements, House and Hogan (49) found that joint stiffness and calcium deposition in soft tissues occurred when the diets were low in magnesium and potassium and high in phosphorus. The clinical signs were most severe on rations that contained 0.9 percent calcium, 1.7 percent phosphorus, 0.04 percent magnesium (about 16 mg per kg daily) and 0.4 percent potassium. During 12 weeks on this diet, growth rate was slow and mortality was 90 percent. When mineral supplementation was changed so that the diet contained approximately 0.35 percent magnesium (about 140 mg per kg) added as MgO and 1.5 percent potassium, the animals made moderate gains in weight, few became stiff, calcium deposition was rare and mortality rate was low.

In a three-month study on the effect of hard water and magnesium sulfate on atherosclerosis in New Zealand rabbits, Neal and Neal (50) found that rabbits given drinking water containing 30,000 ppm MgSO4 (estimated daily magnesium intake, 180 mg per kg) showed no atherosclerosis of the coronary arteries, whereas those given calcium carbonate showed moderate atherosclerosis and the group given distilled water showed the greatest atherosclerosis. All animals were maintained on a chow diet that contained 1 percent added cholesterol and 5 percent butter. Although blood sera from animals which had received magnesium sulfate were clear and differed markedly in appearance from the "milky" sera from animals in the distilled water group, their lipid compositions were essentially the same.
Long-term studies

Maintained on a daily oral program of magnesium oxide (2 mg magnesium per kg) and pyridoxine for five years, 30 of 36 human patients who had suffered from two or more calcium oxalate renal stones yearly during the two prior years, showed either no recurrence or decreased recurrence of stone formation. The investigators were of the opinion that prevention of stone formation involved an effect of the magnesium ion on the solvent properties of the urine (51).

Héroux and Peter (52) fed three-week-old gnotobiotic male Sprague-Dawley rats diets containing three levels of magnesium: high, about 270 mg per 100 g diet; normal, about 52 mg per 100 g diet; and low, about 10 mg per 100 g diet. The ratios of calcium to magnesium and calcium to phosphorus in these diets were 6.30 and 11.50, 60.0 and 2.1 and 1.07 and 1.07, respectively. Rats were caged at 28°C and 6°C and seven-day balance studies were conducted at 69, 240, and 517 days; total magnesium and calcium in the carcass were determined on eight rats of each diet subgroup at 69 and 240 days and four rats of each subgroup at 517 days. At all three ages and at both temperatures, rats receiving the high level of magnesium had highly significant positive balances for magnesium. On the normal magnesium diet, balance at both temperatures was also positive or zero. On the low magnesium diet, the animals at 28°C were in balance at 69 days but by 240 and 517 days they were in negative balance; at 6°C rats on the low magnesium diet had negative balances at all three ages. Because metabolic balance studies are unsuitable as a basis for estimating changes in body composition (53-55), it is not surprising that carcass analyses did not show the magnesium content expected at 240 and 517 days from magnesium retention determined in the balance studies.

Special studies

The effect of magnesium salts on the induction of neoplasms by known carcinogens is equivocal. Labkovskii (56) found that magnesium chloride or sulfate administered daily orally (320 mg magnesium per kg) or subcutaneously (10 mg magnesium per kg), increased the induction of pulmonary adenomas by urethan by 12 to 116 percent in white mice when examined three months after injection. Urethan was injected intraperitoneally twice (four-day interval) at 1 g per kg in 5 percent solution. Magnesium administration was started one day prior to the first injection of urethan and continued for 10 days or was given two weeks prior to urethan and continued for eight weeks. In contrast, Bazikyan and Akimov (57) found that magnesium chloride at a daily dose of 15 mg magnesium per kg reduced the toxicity of 9,10-dimethyl-1, 2-benzanthracene and 1,2,5,6-dibenzanthracene and markedly decreased the yield of skin papillomas induced by these compounds and that of subcutaneous sarcomas induced by a single injection of 3 mg of 1,2,5,6-dibenzanthracene in mature male CC57BR mice. Greatest reduction in skin papillomas resulted when magnesium chloride was given seven days prophylactically and for 53 days following application of the carcinogen which was given at the rate of
50 mg per kg body weight per mouse on alternate days. At 200 days, 41 percent of the mice treated with magnesium chloride had tumors compared with 74 percent in the control group; average number of tumors per mouse was 0.55 ± 0.14 in the magnesium chloride treated group and 0.90 ± 0.17 in the control group.

Subcutaneous doses of magnesium sulfate (80 mg magnesium per kg of body weight) administered to 16 female white rats on alternate days prior to and during early pregnancy lowered fertility and produced defects in the brains and spinal cords of some of the fetuses (58).

Hypermagnesemia occurred in five newborn babies whose mothers received magnesium therapy (10 to 25 g MgSO₄, probably parenterally) for pre-eclampsia. All placental blood samples had high plasma magnesium concentrations. The babies had low rectal temperatures, clinical symptoms of hypocalcemia and were in generally poor condition (59).

Magnesium oxide was not clearly nonmutagenic in microbial assays with or without the addition of mammalian (mice, rat and monkey) metabolic activation tissue homogenates (liver, lung, and testes) using as indicator organisms Saccharomyces cerevisiae D4 and Salmonella typhimurium TA-1535, TA-1537 and TA-1538. Weak responses were observed with S. typhimurium TA-1538 in the presence of primate liver tissue homogenates which the authors considered may be within normal background fluctuations (60). Magnesium stearate exhibited no mutagenic activity in microbial assays with Salmonella typhimurium strains TA-1535, TA-1537, and TA-1538 and Saccharomyces cerevisiae strain D4 with and without rat, mouse, and monkey liver and lung activation preparations (61).

Although no information was available on the biological properties of magnesium stearate and the dibasic and tribasic phosphates, the Select Committee has evaluated the health aspects of stearic acid and calcium stearate (62) and certain phosphate salts (63). The evidence available on the properties of the stearate ion and dibasic and tribasic phosphates, together with that on the magnesium ion presented in this report, does not suggest probable hazard when the magnesium salts of these anions are used as food ingredients.

V. OPINION

Magnesium is a dietary essential. It is involved in myriad metabolic reactions and is necessary for the activity of many intracellular enzymes. Also, with certain other cations, it is important in electrolyte balance. Magnesium is present in fruits, vegetables, grains, milk, meat and fish.
and the natural content of these foods is the major source of the current dietary intake. The Food and Nutrition Board, NRC, has recommended that cereal grain products be fortified with magnesium in view of potential risk of deficiency among significant segments of the population. The usual adult intake is about 300 mg or less per day from all sources and the contribution of food additives to total magnesium intake is very small.

The administration of magnesium sulfate in very high doses to humans occasionally has resulted in severe and even fatal episodes, especially in the presence of pre-existing disease. These occurrences should not be prejudicial to the use of magnesium salts as food ingredients since the dosages given were orders of magnitude greater than the daily dietary intake of magnesium added to food.

While chronic toxicity data are lacking, the status of magnesium as a ubiquitous and essential dietary ingredient for the maintenance of homeostatic and bioenergetic mechanisms leads to the opinion that none of the available evidence suggests any probable hazard when any of the GRAS compounds of magnesium is used as a food ingredient.

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

There is no evidence in the available information on magnesium carbonate, magnesium chloride, magnesium sulfate, magnesium hydroxide, magnesium oxide, magnesium stearate, dibasic magnesium phosphate and tribasic magnesium phosphate that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current and in the manner now practiced, or which might reasonably be expected in the future.
VI. REFERENCES CITED


VII. SCIENTISTS CONTRIBUTING TO THIS REPORT

1. Members of the Select Committee on GRAS Substances:

Joseph F. Borzelleca, Ph.D., Professor of Pharmacology, Medical College of Virginia, Health Sciences Division, Virginia Commonwealth University, Richmond, Va.

Harry G. Day, Sc.D., Professor Emeritus of Chemistry, Indiana University, Bloomington, Ind.

Samuel J. Fomon, M.D., Professor of Pediatrics, College of Medicine, University of Iowa, Iowa City, Iowa.

Bert N. La Du, M.D., Ph.D., Professor and Chairman, Department of Pharmacology, University of Michigan Medical School, Ann Arbor, Mich.

John R. McCoy, V.M.D., Professor of Comparative Pathology, New Jersey College of Medicine and Dentistry, Rutgers Medical School, New Brunswick, N.J.

Sanford A. Miller, Ph.D., Professor of Nutritional Biochemistry, Massachusetts Institute of Technology, Cambridge, Mass.

Gabriel L. Plaa, Ph.D., Professor and Chairman, Department of Pharmacology, University of Montreal Faculty of Medicine, Montreal, Canada.

Michael B. Shimkin, M.D., Professor of Community Medicine and Oncology, School of Medicine, University of California, San Diego, La Jolla, Calif.

Ralph G.H. Siu, Ph.D., Consultant, Washington, D.C.

John L. Wood, Ph.D., Distinguished Service Professor, Department of Biochemistry, University of Tennessee Medical Units, Memphis, Tenn.

George W. Irving, Jr., Ph.D. (Chairman), Research Associate, Life Sciences Research Office, Federation of American Societies for Experimental Biology, Bethesda, Md.
2. LSRO staff:

C. Jelleff Carr, Ph.D., Director
Kenneth D. Fisher, Ph.D., Associate Director
Richard G. Allison, Ph.D., Research Associate
Samuel B. Detwiler, Jr., Research Associate
Andrew F. Freeman, Research Associate
Frederic R. Senti, Ph.D., Research Associate
John M. Talbot, M.D., Research Associate

Report submitted by:

March 14, 1977
Date

George W. Irving, Jr., Chairman
Select Committee on GRAS Substances