EVALUATION OF THE HEALTH ASPECTS OF CALCIUM PANTOTHENATE, SODIUM PANTOTHENATE, AND D-PANTOTHENYL ALCOHOL AS FOOD INGREDIENTS

1978

Prepared for

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

Contract No. FDA 223-75-2004
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Life Sciences Research Office
Federation of American Societies for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014
NOTICE

This report is one of a series concerning the health aspects of using the Generally Recognized as Safe (GRAS) or prior sanctioned food substances as food ingredients, being made by the Federation of American Societies for Experimental Biology (FASEB) under contract no. 223-75-2004 with the Food and Drug Administration (FDA), U.S. Department of Health, Education, and Welfare. The Federation recognizes that the safety of GRAS substances is of national significance, and that its resources are particularly suited to marshalling the opinions of knowledgeable scientists to assist in these evaluations. The Life Sciences Research Office (LSRO), established by FASEB in 1962 to make scientific assessments in the biomedical sciences, is conducting these studies.

Qualified scientists were selected as consultants to review and evaluate the available information on each of the GRAS substances. These scientists, designated the Select Committee on GRAS Substances, were chosen for their experience and judgment with due consideration for balance and breadth in the appropriate professional disciplines. The Select Committee's evaluations are being made independently of FDA or any other group, governmental or nongovernmental. The Select Committee accepts responsibility for the content of each report. Members of the Select Committee who have contributed to this report are named in Section VII.

Tentative reports are made available to the public for review in the Office of the Hearing Clerk, Food and Drug Administration, after announcement in the Federal Register, and opportunity is provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the substances covered by the report. The data, information, and views presented at the hearing are considered by the Select Committee in reaching its final conclusions. Reports are approved by the Select Committee and the Director of LSRO, and subsequently reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent society of FASEB) under authority delegated by the Executive Committee of the Federation Board. Upon completion of these review procedures the reports are approved and transmitted to FDA by the Executive Director of FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of all of the individual members of its constituent societies.

Kenneth D. Fisher, Ph.D., Director
Life Sciences Research Office
FASEB
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I. INTRODUCTION

This report concerns the health aspects of using calcium pantothenate, sodium pantothenate, and D-pantothenyl alcohol as food ingredients. It has been based partly on the information contained in a scientific literature review (monograph) furnished by FDA (1), which summarizes the world's scientific literature from 1920 through 1974.* To assure completeness and currency as of the date of this report this information has been supplemented by searches of over 30 scientific and statistical reference sources and compendia that are generally available; use of new, relevant books and reviews and the literature citations contained in them; consideration of current literature citations obtained through computer retrieval systems of the National Library of Medicine; searches for relevant data in the files of FDA; and by the combined knowledge and experience of members of the Select Committee and the LSRO staff. In addition, an announcement was made in the Federal Register of June 13, 1978 (43 FR 25487-25489) 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 calcium pantothenate, sodium pantothenate and D-pantothenyl alcohol as food ingredients. The Select Committee received no requests for such a hearing on calcium pantothenate, sodium pantothenate and D-pantothenyl alcohol.

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321 (s)], GRAS substances are exempt from the premarketing clearance that is required for food additives. It is stated in the Act and in the Code of Federal Regulations (2) [21 CFR 170.3 and 170.30] that GRAS means general recognition of safety by experts qualified by scientific training and experience to evaluate the safety of substances on the basis of scientific data derived from published literature. These sections of the Code also indicate that expert judgment is to be based on the evaluation of results of credible toxicological testing or, for those substances used in food prior to January 1, 1958, on a reasoned judgment founded in experience with common food use, and is to take into account reasonably anticipated patterns of consumption, cumulative effects in the diet, and safety factors appropriate for the utilization of animal experimentation data. FDA (2) recognizes further [21 CFR 170.30] that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

*The document (PB-234 892/8) 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 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 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 Committee, there are insufficient data upon which to base a conclusion. The Committee is aware that its conclusions will need to be reviewed as new or better information becomes available.

In this context, the LSRO Select Committee on GRAS Substances has reviewed the available information on calcium pantothenate, sodium pantothenate, and D-pantothenyl alcohol 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

\[
\text{CH}_3 \quad \text{OH} \quad \text{O} \\
\text{OH—CH}_2—\text{C—CH—C—NH—CH}_2—\text{CH}_2—\text{COOH} \\
\text{CH}_3
\]

Pantothenic acid, \( \text{OH—CH}_2—\text{C—CH—C—NH—CH}_2—\text{CH}_2—\text{COOH} \), is one of the vitamins of the B complex. It is a component of coenzyme A which is involved in many acetylation reactions in tissues; e.g., the conversion of choline to acetylcholine, acetate to acetoacetate and oxalacetate to citrate (3, 4). The vitamin has been demonstrated to be essential for monkeys and many other animal species (4). A deficiency syndrome for it has been induced in human subjects (5). It is widely distributed in nature and is found throughout the animal and plant kingdoms. Particularly good sources are liver, meat, cereal grains, milk, egg yolk and fresh vegetables. Only the natural, D (dextrorotatory) isomer has vitamin activity (4).

Manifestations of pantothenic acid deficiency have been reviewed by Sauberlich (4). In the chick, these include dermatitis, fatty liver, degeneration of the spinal cord, and involution of the thymus. Deficiency in rats is characterized by dermatitis, achromotrichia, adrenal necrosis, spastic gait, anemia, leukopenia, gonadal atrophy, and impaired ability to form antibodies. Congenital malformations may occur in offspring of pantothenate-deficient rats. Deficiency in dogs and monkeys results in fatty livers and central nervous system disorders.

Experimental production of pantothenic acid deficiency in adult human volunteers by feeding of the antagonist, \( \alpha \)-methyl pantothenate (5, 6) was associated with malaise, vomiting, abdominal cramps, tenderness of the heels, fatigue, and insomnia.

The Code of Federal Regulations lists calcium pantothenate [21 CFR 182.5212], sodium pantothenate [21 CFR 182.5772], and D-pantothenyl alcohol [21 CFR 182.5580] as generally recognized as safe (GRAS) for use as nutrients and/or dietary supplements when used in accordance with good manufacturing practice (2). The stereoisomeric forms of calcium and sodium pantothenate are not specified in the code. Calcium pantothenate is the form commonly added to food. Solutions of calcium pantothenate are not sufficiently stable to withstand autoclaving and, therefore, the relatively heat-stable D-pantothenyl alcohol, which is converted to pantothenate in mammalian systems, is preferred for some uses (3).

The calcium chloride double salt of calcium pantothenate has been cleared for use in foods for special dietary uses [21 CFR 172.330] when the additive is of the D or DL form (2).

D-pantothenamide [21 CFR 172.335] is a regulated food additive listed as a source of pantothenic acid activity in foods for special dietary use not in
excess of that reasonably required to produce its intended effect (2). Only the GRAS food ingredients, calcium and sodium pantothenate and D-pantothenyl alcohol are evaluated in this report.

The Food Chemicals Codex (7) lists the following food-grade specifications for D-calcium pantothenate and DL-calcium pantothenate, and D-pantothenyl alcohol: D-calcium pantothenate should contain not less than 90.0 percent and not more than the equivalent of 110.0 percent of dextrorotatory calcium pantothenate \( \left( \text{C}_{18}\text{H}_{32}\text{CaN}_{2}\text{O}_{10} \right) \) calculated on the dried basis, the calcium content should be not less than 8.2 percent and not more than 8.6 percent after drying and heavy metal content should not exceed 20 ppm (as lead); DL-calcium pantothenate should contain not less than 42.5 percent of dextrorotatory calcium pantothenate calculated on the dried basis, and the specifications for calcium and heavy metal content are the same as those for D-calcium pantothenate; D-pantothenyl alcohol (dexpantenol) should contain not less than 98.0 percent and not more than 102.0 percent D-pantothenyl alcohol \( \left( \text{C}_{9}\text{H}_{18}\text{NO}_{4} \right) \), calculated on the anhydrous basis, not more than 1 percent aminopropanol, not more than 3 ppm arsenic, and not more than 10 ppm heavy metals (as lead). The Codex does not list specifications for sodium pantothenate.
III. CONSUMER EXPOSURE DATA

A survey of food manufacturers by a National Research Council (NRC) subcommittee (8) indicated per capita consumption of 0.08 mg per day for supplemental calcium pantothenate added to processed food based on poundage data adjusted to reflect the subcommittee's estimate that survey responses accounted for about 60 percent of total poundage used (Table I). A 6.6-fold increase in usage was reported from 1960 to 1970. The estimated daily per capita consumption of calcium pantothenate added to foods may be compared with the estimates of total intake of pantothenes from all food sources of 5 to 19 mg daily (9, 10) and with a statement of the Food and Nutrition Board that "A daily intake of 5-10 mg is probably adequate for all adults; the upper level is suggested for pregnant and lactating women" (11).

The NRC survey revealed that no manufacturers reported adding sodium pantothenate or D-pantothenyl alcohol to food (8).

The NRC subcommittee survey (8) also provided information on the level of addition of calcium pantothenate to foods in several food categories (Table II). Manufacturers were surveyed by questionnaire concerning the usual levels of addition of calcium pantothenate to foods. Based on information supplied by those manufacturers who reported adding the substance to at least one food in a category, a weighted mean was calculated for percentage addition of calcium pantothenate to food products in that category. An entry in Table II does not mean that all foods in that category contain added pantothenates.

The subcommittee also calculated possible average daily intakes based on Market Research Corporation of America data on 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 foods within a category contained calcium pantothenate at the level shown in Table II. As pointed out by the subcommittee, such assumptions are likely to lead to overestimates of intake, often by considerable margins, as explained in detail in Section XI of the subcommittee's report (8). It is, therefore, not surprising that estimated average intakes of calcium pantothenate calculated by this method are high. For example, the estimated average consumption of calcium pantothenate added to foods is 13.3 mg per day for persons two years of age or older when calculated by this method. This value is more than 150 times the estimated per capita consumption (0.08 mg per day) based on pounds of calcium pantothenate reported by manufacturers to be added to foods. The Select Committee believes the value of 0.08 mg per day to be the more accurate estimate of the per capita consumption of calcium pantothenate added to food.
TABLE I
Consumption of Calcium Pantothenate Based on Total Quantity Used Annually in Foods (8)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Relative amounts used&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Total used&lt;sup&gt;b&lt;/sup&gt; (1970) kg</th>
<th>Per capita intake calculated from quantity used&lt;sup&gt;c&lt;/sup&gt; mg/person/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium pantothenate</td>
<td>6.6</td>
<td>6058</td>
<td>0.08</td>
</tr>
</tbody>
</table>

<sup>a</sup> Based only on reports from those respondents to the National Research Council (NRC) survey who submitted information for 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.
<table>
<thead>
<tr>
<th>Food category</th>
<th>Level of addition (weighted mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>percent</td>
</tr>
<tr>
<td>Baked goods, baking mixes</td>
<td>0.005</td>
</tr>
<tr>
<td>Milk products</td>
<td>0.001</td>
</tr>
<tr>
<td>Meat products</td>
<td>0.006</td>
</tr>
<tr>
<td>Poultry products</td>
<td>0.006</td>
</tr>
<tr>
<td>Fish products</td>
<td>0.006</td>
</tr>
<tr>
<td>Snack foods</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Beverages, nonalcoholic</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reconstituted vegetable proteins</td>
<td>0.002</td>
</tr>
<tr>
<td>Dairy products analogs</td>
<td>0.001</td>
</tr>
<tr>
<td>Baby formulas</td>
<td>0.001</td>
</tr>
</tbody>
</table>
IV. BIOLOGICAL STUDIES

Absorption and metabolism

Studies with rats have demonstrated considerably better absorption of single oral doses of pantothenyl alcohol than of calcium pantothenate (12-14). During the first 24 hours after administration of a single oral dose of 1.0 mg of pantothenyl alcohol (isomeric form not stated), Braekkan (12) found that 0.80 mg of pantothenic acid was excreted in the urine. After administration of an oral dose of 4 mg of pantothenic acid, 64 percent (2.57 mg) was excreted in the urine. By contrast, only 0.32 mg of pantothenic acid was excreted in the urine during the 24 hours after administration of 1 mg of calcium pantothenate and only 0.98 mg (about 25 percent) after administration of 4 mg. Daily pantothenate excretion by undosed rats was about 0.12 mg. After administration of single doses of up to 4.0 mg of pantothenyl alcohol or calcium pantothenate intraperitoneally, urinary excretion in 24 hours accounted for as much as 80 percent of the administered doses. Rubin et al. (13) reported that other components of the diet had little influence on absorption of pantothenyl alcohol or calcium pantothenate by adult male Sprague-Dawley rats.

Taylor et al. (15) showed a species difference in pantothenate excretion between the rat and the dog. Dogs given 7 mg (0.8 mg per kg) orally of radioactive sodium pantothenate excreted only 0.5 percent of the dose as unchanged pantothenate in the urine, all of it within 24 hours of dosing; whereas 40 percent was excreted as the β-glucuronide in the 7-day urine. Two rats given 330 μg (1.6 mg per kg) of the labeled substance excreted 27 percent of the dose as pantothenate in the 7-day urine but no pantothenyl β-glucuronide was detected.

In a later paper, Taylor and coworkers (16) administered an oral dose of 6.7 mg of radiolabeled sodium pantothenate to two adult male beagles. In the 7 days following dosing, 48 to 57 percent of the dose was excreted in the urine and 17 to 26 percent in the feces. When the same dose was administered intravenously, 33 to 44 percent was found in the urine and 7 to 8 percent in the feces. About 85 to 90 percent of the oral dose was calculated to have been absorbed. Almost all of the radioactive material excreted in the urine was pantothenyl β-glucuronide; less than 1 percent was the unchanged pantothenate. The radiolabeled material found in the feces was the unchanged pantothenate. After oral administration of sodium pantothenate, maximum plasma levels of radioactivity occurred about 2 to 2.5 hours after dosing. The plasma half-life was 15 to 17 hours.

After oral administration of 100 mg of calcium pantothenate (isomeric form not stated) to adult humans, urinary excretion was found to be maximal during the first 4 hours with about 20 percent of the dose being excreted in this time period, apparently as pantothenate (17). The authors did not specify
experimental methods however, so it is not possible to know with certainty whether conjugated derivatives or unchanged pantothenate was excreted.

Administration of calcium pantothenate to pregnant rats increased pantothenic acid concentrations of fetal blood and tissues making it apparent that the substance readily crosses the placenta (18, 19). Animals receiving the stock diet (providing 450-600 µg of pantothenic acid per day) had offspring with blood pantothenic acid levels of about 450 µg per 100 ml. Animals receiving synthetic diets providing 0, 100, or 1000 µg per day of pantothenic acid had offspring with blood pantothenate levels of about 295, 500, and 2200 µg per 100 ml respectively.

The literature on the biosynthesis of coenzyme A from pantothenate was reviewed by Plaut et al. (20). The first step in the formation of coenzyme A from pantothenate is thought to be phosphorylation of the hydroxyl group of pantothenate catalyzed by the enzyme pantothenate kinase (21, 22). This enzyme catalyzes the phosphorylation of D-pantothenate by adenosine triphosphate but is not active with L-pantothenate, which is a competitive inhibitor of D-pantothenate kinase (23). The Select Committee is not aware of any investigations of the possible toxicity of L-pantothenate ingestion in the absence of D-pantothenate.

Pantothenyl alcohol as such has no vitamin activity but in mammalian systems it is converted into the active vitamin (24). Pantothenate kinase can catalyze the phosphorylation of D-pantothenyl alcohol. However, in vivo the first step in formation of the active vitamin may be oxidation of D-pantothenyl alcohol to D-pantothenate by alcohol dehydrogenase since D-pantothenyl alcohol, but not D-pantothenyl 4-phosphate, is a substrate for rat liver alcohol dehydrogenase (25, 26).

**Acute toxicity**

The acute toxicity of D-calcium pantothenate was studied by Unna and Greslin (27) in mice, rats, dogs, and one monkey. Results of studies with 180 mice and 110 rats are given in Table III. Deaths appeared to be associated with prostration and respiratory failure. None of the rats given 10 g per kg of body weight orally demonstrated any signs of toxicity. No evidence of toxicity was noted in five dogs and one monkey after oral dosage of 1 g per kg.

Weiss et al. (28) reported that with intravenous administration of D-pantothenyl alcohol the LD50 was 7 g per kg for mice and 4 g per kg for rabbits (Table III). The number of animals studied was not mentioned. The authors stated that all the mice survived an intravenous dose of 6.25 g per kg and all the rabbits survived an intravenous dose of 3 g per kg.

None of six mice given 10 g per kg orally of D-pantothenyl alcohol died, whereas all six mice given 20 g per kg died (Table III) (29). Intravenous
### TABLE III

Acute Toxicity (LD₅₀) of Calcium Pantothenate and D-Pantothenyl Alcohol in Animals

<table>
<thead>
<tr>
<th>Substance</th>
<th>Species</th>
<th>Weight</th>
<th>Route</th>
<th>LD₅₀</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium D-pantothenate</td>
<td>Mice</td>
<td>20-22</td>
<td>or</td>
<td>10.0</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>sc</td>
<td>2.7</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ip</td>
<td>0.92</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>iv</td>
<td>0.91</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>iv</td>
<td>0.685</td>
<td>29</td>
</tr>
<tr>
<td>Rats</td>
<td></td>
<td>150-200</td>
<td>or</td>
<td>&gt;10.0</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>sc</td>
<td>3.4</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ip</td>
<td>0.82</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>iv</td>
<td>0.83</td>
<td>27</td>
</tr>
<tr>
<td>D-pantothenyl alcohol</td>
<td>Mice</td>
<td></td>
<td>or</td>
<td>15.0</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>iv</td>
<td>7.0</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>iv</td>
<td>&gt;10.0</td>
<td>29</td>
</tr>
<tr>
<td>Rabbits</td>
<td></td>
<td></td>
<td>iv</td>
<td>4.0</td>
<td>28</td>
</tr>
</tbody>
</table>
doses of D-pantothenyl alcohol (4 to 10 g per kg of body weight) were given to 27 mice. The LD$_{50}$ was found to be greater than 10 g per kg; three of nine mice died after receiving 10 g per kg (29). In studies of 24 mice receiving intravenously 500 to 800 mg per kg of calcium D-pantothenate, the LD$_{50}$ was found to be 685 mg per kg. No deaths occurred in rabbits given intravenous injections of 0.1, 0.5, 1, 2, 4, 8, or 10 g per kg (2 animals at each level) of D-pantothenyl alcohol. Neither were deaths reported in nine dogs given intravenous injections of 2 to 10 g per kg of D-pantothenyl alcohol (29).

Wirtschafter and Walsh (30) administered sodium pantothenate intramuscularly to one mature Long-Evans rat in a single dose of 750 mg and in five daily doses of 250 mg to one other rat. They reported microscopic evidence of fatty changes in the liver and increased activity of serum glutamic oxaloacetate transaminase. Body weights of the rats were not stated, but if a weight of 250 g is assumed, the dosage of sodium pantothenate may have been about 3.0 g per kg in the single dose experiment and about 1.0 g per kg for each of the daily doses in the five-dose experiment.

Schwartz and Bagdon (31) injected Sprague-Dawley rats with single intramuscular doses of 0.1, 0.2, or 2.0 mg per kg of sodium pantothenate or D-pantothenyl alcohol. Two groups of rats were used for each compound and at each dosage level. One group was in the 110 to 120 g weight range and the other group weighed between 225 and 275 g; there were 10 animals per group. The animals were sacrificed 96 hours after dosing. Compared with controls, there were no significant effects of the compounds on body or liver weights, nor on serum glutamic oxaloacetate transaminase or serum glutamic pyruvate transaminase activities. Rats weighing 110 to 120 g, given 2.0 or 0.2 g per kg of D-pantothenyl alcohol, showed a slight but statistically significant increase in lipid content of the liver, an effect not observed in the group weighing 225 to 275 g.

**Short-term studies**

Unna and Greslin (27) reported normal growth with no evidence of toxicity in two groups of 20 young rats each fed either 50 mg or 200 mg (about 500 or 2000 mg per kg) of D-calcium pantothenate per day for 190 days. The species of rat and other details were not stated. Autopsies at the end of the feeding period showed no gross or microscopic changes in the organs (further details not given). Weaned offspring of the group receiving 50 mg of calcium pantothenate daily were given the same daily dose and their weights increased at the same rate as controls. Similarly, no evidence of toxicity was observed in six dogs fed 50 mg (about 5 mg per kg) of D-calcium pantothenate daily for 180 days or in four monkeys, 2.5 to 4 kg body weight, given 1 g (250 to 400 mg per kg) of D-calcium pantothenate daily for 180 days.
Weiss et al. (28) found similar rates of growth in 24 rats fed 2 mg (about 20 mg per kg) of pantothenyl alcohol daily for 6 months and in 12 control rats. An unspecified number of rats fed 20 mg (200 mg per kg) and dogs fed 500 mg (50 mg per kg assuming 10 kg dogs) of pantothenyl alcohol daily for 3 months also failed to demonstrate evidence (including "histopathologic changes") of toxicity. The authors stated that hemoglobin concentration, erythrocyte and leukocyte counts, and concentrations of sugar in blood and urea nitrogen in serum were unaffected, but gave no specific data.

Weiss et al. (28) also determined the effect of pantothenate feeding on the tissue levels of the substance. The total pantothenate content of the liver, kidney, heart and spleen was measured after daily doses of 2 mg D-pantothenyl alcohol (20 mg per kg) or 2.3 mg (23 mg per kg) of calcium pantothenate (isomeric form not stated) were fed to rats for 24 or 45 days or for 5 to 6 months. Liver or spleen pantothenate content was not increased over controls in any of the experimental groups. There were 20 and 32 percent increases in heart pantothenate content after 6 months' feeding with D-pantothenyl alcohol and calcium pantothenate, respectively. There were slight increases in the kidney pantothenate content of the experimental groups at 24 and 45 days and a large increase of 43 percent in the group fed D-pantothenyl alcohol for 6 months. A test for D-pantothenyl alcohol showed none was present in the livers of the animals dosed with the substance for 6 months.

A 90-day feeding study was carried out using young CB strain rats fed doses of 20, 50, or 200 mg per kg per day of D-calcium pantothenate, D-pantothenyl alcohol, or DL-pantothenyl alcohol in their drinking water (29). Six male and six female animals (average weight about 100 g) were used for each feeding group and the control group. No major differences between control and experimental groups were noted with respect to growth, mortality, hematologic findings, and final weights of vital organs. Mild eosinophilia was present in some experimental animals, but the investigators stated that it was not clear if the condition was treatment-related. The final weight of the adrenal glands was higher in male animals and lower in females receiving calcium pantothenate than in controls. The effect was most marked (24 percent increased adrenal weight) at the 50 mg per kg level in the males and the 200 mg per kg level in the females (17 percent decreased adrenal weight). Considering the small number of animals tested and the different direction of the weight changes between the sexes, the significance of the results is doubtful. Histopathological studies indicated that there were no marked toxic changes related to treatment. However, with DL-pantothenyl alcohol at 200 mg per kg there was slight cloudy swelling of the kidney tubular cells; with D-pantothenyl alcohol at 20 mg per kg part of the kidney showed cloudy swelling; and at a dosage of 200 mg per kg of calcium pantothenate, the animals showed slight hyperemia of the spleen. The report stated that the changes were not found in every animal in the group and were not marked.
Long-term studies

Pelton and Williams (32) gave 33 young male and female C-57 black mice laboratory chow supplemented with approximately 300 µg daily (about 20 mg per kg) of calcium pantothenate (isomeric form not indicated) in drinking water; there were 41 control animals. Mean life span of mice given the supplement was 653 days and that of the control mice was 550 days. This difference was statistically significant. After approximately 250 days of age, body weights of the supplemented mice were slightly greater than those of controls. Neither gross nor microscopic pathological examinations of the animals were conducted.

Clinical studies

In studies on 15 adult human subjects, Spies et al. (33) reported that intravenous injection of 100 mg (about 1.6 mg per kg) of either sodium or calcium pantothenate (isomeric forms not indicated) was without effect on blood pressure, pulse, temperature or respiration.

Intramuscular administration of D-pantothenyl alcohol has been tried for prevention and treatment of postoperative paralytic ileus; several double-blind studies (34-38) failed to demonstrate a beneficial effect. However, no signs of toxicity were reported following several days treatment at about 2 g per day in divided doses.

Goldman (39, 40) reported observations of patients with disseminated lupus erythematosus given oral doses of pantothenyl alcohol or calcium pantothenate (isomeric forms not indicated) 1 to 2 g per day for as long as 6 months, and other patients were given daily doses of pantothenyl alcohol as high as 10 g for unspecified periods of time. He stated that improvement in manifestations of the disease occurred (although there were no controls), and no signs of toxicity were observed. Welsh (41) treated patients with lupus erythematosus and granuloma annulare with up to 10 g per day of pantothenyl alcohol for as long as three years. Other than transient nausea, no ill effects were observed. Welsh also treated some patients with up to 2 g per day of D-calcium pantothenate and up to 10 g per day of DL-calcium pantothenate. No side-effects of the treatment were noted.

Special studies

Gábor et al. (42) reported that intravenous administration of 10 to 200 mg per kg pantothentic acid (isomeric form not indicated) to cats did not affect blood pressure. However, when blood pressure was elevated by infusion of epinephrine, the administration of pantothentic acid had a dose-related potentiating effect on blood pressure. In addition, administration of pantothenic acid in doses of 1 mg per kg or more potentiated the depressant effect of acetylcholine on blood pressure, but this effect was not dose-related.
No evidences of teratogenicity or fetotoxicity were observed in the offspring of Wistar strain female rats fed a semisynthetic diet providing 1 mg (about 5 mg per kg) of calcium pantothenate daily (18, 19). The animals were fed the diet prior to mating and throughout gestation.

Grabowski (43) injected 0.02 ml of sodium chloride (0.0145 M), or 0.01 ml of calcium pantothenate (0.01 M) or calcium chloride (0.01 M) into the yolk sac of 542 two-day-old chick embryos. Death rates in two days were 24 percent, 30 percent, and 36 percent, respectively. Abnormalities were present in 3 percent of the sodium chloride-injected controls, in 17 percent of those injected with calcium pantothenate and in 14 percent of those injected with calcium chloride. It was concluded that the calcium ion rather than pantothenate caused the abnormalities.

Sodium D-pantothenate was found not to exhibit mutagenic activity in in vitro microbial plate and suspension assays, with and without metabolic activation. The microorganisms used were Saccharomyces cerevisiae strain D4 and Salmonella typhimurium strains TA-1535, -1537, -1538, -98, and -100 (44).

The Select Committee has found no pertinent studies of the possible carcinogenicity of the pantothenates.
V. OPINION

Pantothenates occur in all tissues of the body and are essential for normal metabolic function. Daily consumption of calcium pantothenate added to foods by processors in the United States appears to be less than 0.08 mg per capita (1.3 μg per kg), a value that probably also represents total per capita daily consumption of pantothenates added to foods since sodium pantothenate and pantothenyl alcohol do not appear to be used by food processors.

It is estimated that the usual adult diet provides approximately 5 to 19 mg (83 to 316 μg per kg) of naturally occurring pantothenates daily. Animals of several species given 100 mg per kg or more of calcium pantothenate daily for several months showed no evidence of toxicity. Adult patients with disseminated or discoid lupus erythematosus receiving doses of 1 g or more daily (16.6 mg per kg) for several months manifested no evidence of toxicity. Although the evidence is scanty, there appears to be no reason to suspect teratogenicity, fetotoxicity or carcinogenicity from intakes considerably greater than those likely to be obtained from foods.

There is little information concerning the metabolism of L-pantothenic acid or its salts, although animal and human studies of administration of racemic mixtures of calcium or sodium pantothenate demonstrate no untoward effects at doses considerably higher than could be reasonably expected from pantothenates added to food.

There are no specifications listed for food grade sodium pantothenate. The Select Committee believes such specifications should be developed even though there appears to be no current use of sodium pantothenate.

The Select Committee has weighed the foregoing and concludes that:

There is no evidence in the available information on D-pantothenyl alcohol, D- or DL-calcium pantothenate or D-or DL-sodium pantothenate 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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The Select Committee expresses its appreciation to Hoffmann-LaRoche, Inc., Nutley, N.J. 07110, who contributed information and data.

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OCT 18 1972
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