EVALUATION OF THE HEALTH ASPECTS OF ASCORBIC ACID, SODIUM ASCORBATE, CALCIUM ASCORBATE, ERYTHORBIC ACID, SODIUM ERYTHORBATE, AND ASCORBYL PALMITATE AS FOOD INGREDIENTS

1979

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 L-ascorbic acid, calcium and sodium L-ascorbates, erythorbic acid (D-isoascorbic acid), sodium erythorbate (sodium D-isoascorbate) and ascorbyl palmitate (palmitoyl L-ascorbate) as food ingredients. It has been based partly on the information contained in scientific literature reviews (monographs) furnished by FDA (1, 2) which summarize 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 on March 9, 1979 (44 FR 13080) 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 ascorbic acid, sodium ascorbate, calcium ascorbate, erythorbic acid, sodium erythorbate, and ascorbyl palmitate as food ingredients. One request was received. The Select Committee held a hearing on July 16, 1979. B.S. Gould, Ph.D., of the Massachusetts Institute of Technology, Cambridge, Mass., presented data which were considered by the Select Committee in reaching its final conclusion.**

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 (3) [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

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*The documents (PB-241 969/5ST and PB-223 866/5ST) are available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.

appropriate for the utilization of animal experimentation data. FDA (3) recognizes further [21 CFR 170.30] 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 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 L-ascorbic acid, calcium and sodium L-ascorbates, erythorbic acid (D-isoascorbic acid), sodium erythorbate (sodium D-isoascorbate) and ascorbyl palmitate (palmitoyl L-ascorbate), 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 Cosmetics Act.
II. BACKGROUND INFORMATION

Ascorbic acid (L-ascorbic acid; vitamin C), its sodium and calcium salts, and erythorbic (D-isoascorbic) acid and its sodium salt are white or slightly yellow crystalline solids. They are soluble in water, but of limited to slight solubility in ethyl alcohol; for example, 1 g ascorbic acid dissolves in about 30 ml alcohol (4). Structural formulas of L-ascorbic acid and its stereoisomers are given in Figure I.

Ascorbyl palmitate is a white or yellowish white solid at room temperature. It is very slightly soluble in water, and 1 g dissolves in about 4.5 ml ethyl alcohol. With the exception of sodium erythorbate, the Food Chemicals Codex (5) lists specifications for the ascorbates covered in this report and sets limits of impurities as shown in Table I.

Ascorbic acid is present in nutritionally useful amounts in many edible plants, especially rapidly growing leafy vegetables, fruits, tomatoes and potatoes (6). Foods of animal origin as usually consumed are generally poor sources of the vitamin (7).

Federal regulations (3) list as GRAS substances the following ascorbates for use as chemical preservatives in foods: ascorbic acid (21 CFR 182.3013), sodium ascorbate (21 CFR 182.3731), erythorbic acid (21 CFR 182.3041), calcium ascorbate (21 CFR 182.3189), and ascorbyl palmitate (21 CFR 182.3149). Ascorbic acid is GRAS as a nutrient and/or dietary supplement (21 CFR 182.5013), and sodium isoascorbate (sodium erythorbate) is considered unpublished GRAS as a food preservative and/or antioxidant (8,9).

In addition, some of these substances are otherwise regulated by other sections of the Code (3); for example, ascorbic acid is approved as a dough conditioner in cereal flours (tolerance 200 ppm), breads and other bakery products (21 CFR 136 and 137); as an acidulant in frozen desserts (21 CFR 135); as a preservative in artificially sweetened fruit jellies and preserves (21 CFR 150); and as an optional ingredient in canned artichokes and mushrooms (21 CFR 155.200). Ascorbic acid, erythorbic acid, sodium ascorbate and sodium erythorbate are regulated by the U.S. Department of Agriculture (10) as curing accelerators for pork and beef and comminuted meat products in 9 CFR 318.7 (c) (4). A recent ruling by that Department (11) requires that sodium ascorbate or sodium erythorbate be used at levels of 550 ppm in the preparation of bacon to inhibit formation of nitrosamines.

When vitamin C was isolated and characterized in the late 1920's and early thirties, it was named ascorbic acid (12). Of the four stereoisomeric
Structural Formulas of L-Ascorbic Acid and its Stereoisomers (Fischer Convention)

\[
\begin{align*}
\text{L-ASCORBIC ACID} & \quad \text{D-ASCORBIC ACID} \\
\text{L-ISOASCORBIC ACID} & \quad \text{D-ISOASCORBIC ACID}
\end{align*}
\]
### TABLE I

Specifications of Food Grade Ascorbic Acid and Other Ascorbates

<table>
<thead>
<tr>
<th>Compound</th>
<th>Assay percent</th>
<th>Arsenic ppm</th>
<th>Heavy metals (as lead) ppm</th>
<th>Lead ppm</th>
<th>Other impurities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascorbic acid</td>
<td>99.0%</td>
<td>3</td>
<td>20</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>C₆H₆O₆</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium ascorbate</td>
<td>90.0 - 101.0%</td>
<td>3</td>
<td>20</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>C₆H₇NaO₆</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythorbic acid</td>
<td>99.0%</td>
<td>3</td>
<td>20</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>C₆H₆O₆</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium ascorbate</td>
<td>98.0%</td>
<td>3</td>
<td>10</td>
<td>-</td>
<td>Oxalate, passes test</td>
</tr>
<tr>
<td></td>
<td>C₁₃H₁₄CaO₁₃•2H₂O</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascorbyl palmitate</td>
<td>95.0%</td>
<td>3</td>
<td>10</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>C₂₃H₃₆O₇</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2Data taken from Food Chemicals Codex (5).
ascorbic acids (Figure I), only L-ascorbic acid has significant vitamin C activity. The vitamin C activity of ascorbyl palmitate is approximately equal to that of L-ascorbic acid (2). The natural and synthetic L-ascorbic acids are equivalent in vitamin C activity.

Ascorbic acid is available commercially as the L-acid and its sodium salt (13). The only related compounds which are clearly active become so through metabolic conversion to ascorbic acid in the body. Dehydroascorbic acid is fully as active as ascorbic acid since ascorbic acid oxidase in the body functions in maintaining an equilibrium between these two compounds (12).

The fact that a compound containing the ascorbic acid enediol ring system can be synthesized from a hexulosonic acid by means of an acid or from the corresponding ester by the action of an alkali is the basis for modern manufacturing processes for L-ascorbic acid (14). The most widely used process is the L-sorbose synthesis in which L-sorbitol, derived from D-glucose by hydrogenation, is converted to L-sorbose by fermentation with Acetobacter suboxidans. Introduction of a carboxyl group at C₁ while the L-sorbose is in the diacetone derivative form yields diacetone-2-keto-L-gulonic acid. Removal of acetone and heating in an acid medium yield L-ascorbic acid, which may be crystallized in high purity (4, 14, 15).

The ascorbates are used as inhibitors of enzymatic browning or as preservatives (antioxidants) in small concentrations in a variety of foods and beverages including concentrated milk products, certain meat products, pickling brine for pork and beef cuts, baked goods, soft and hard candies, fats and oils, gravies, breakfast cereals and processed fruits and vegetables (2). In a review of the properties and uses of ascorbic acid and isoascorbic (erythorbic) acid as antioxidants in foods and food processing, Borenstein (16) concluded that ascorbic acid is the more desirable antioxidant because it is more efficient and more stable in aqueous systems.

Ascorbic acid or its salts are essential nutrients, and all persons consume ascorbic acid as a normal constituent of foods; many obtain it or related ascorbates as components of vitamin preparations and as added ingredients or supplements in certain foods or beverages. It has been suggested that ascorbic acid is useful in the prevention and treatment of the common cold and other disorders (17); however, such uses are not evaluated in this report.
III. CONSUMER EXPOSURE DATA

A survey of food manufacturers by a National Research Council (NRC) subcommittee (18) has provided information on the level of addition of ascorbic acid and other ascorbates to foods in several categories as given in Table II. Based on information supplied by manufacturers who reported adding the substance in question (ascorbic acid or one of the ascorbates) to at least one food in a category, weighted means were calculated for the usual level of addition to the food category (Table II). Some of the values in Table II appear high. For example, it seems unlikely that many items in the baked goods category have a level of added ascorbic acid of 0.028 percent or of sodium ascorbate of 0.094 percent. Alcoholic beverages rarely contain added ascorbic acid. In the case of baby formulas, the concentrations of ascorbic acid listed in the Physicians' Desk Reference (19) are approximately one-half those listed in Table II. Values in Table II may apply to concentrated liquid formulas (133 kcal/100 ml) rather than to formulas as fed (67 kcal/100 ml). Compositional tables supplied by manufacturers of strained and junior foods for infants do not confirm the addition of ascorbic acid to baby combination dinners. On the other hand, the addition of 0.054 percent erythorbic acid to at least one meat product (bacon) has been confirmed (20).

The NRC subcommittee estimated possible average daily intakes of ascorbic acid and ascorbates (Table III) based on Market Research Corporation of America data on mean frequency of eating by food category and age, U.S. Department of Agriculture data on mean portion size of foods in these categories and the assumption that all food products within the category contain the substance in question at the level indicated in Table II. Such an assumption is likely to lead to overestimates of intake. The NRC subcommittee has recognized that in the case of most such calculations, estimates of intakes of the substance in question are overstated, often by considerable margins. Because of factors detailed in Section XI of the subcommittee's report (18), the possible average dietary intakes estimated in this manner are likely to be much greater 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.

In the case of ascorbic acid and ascorbates, the estimates made in this manner do appear to be high (Table III). For individuals over 2 years of age, the estimated average daily intake of added ascorbic acid was 213 mg per day and that of sodium ascorbate, 338 mg per day. Intakes of erythorbic acid and sodium erythorbate were 49 and 32 mg per day, respectively.
### Table II

**Level of Addition (Percent) of Ascorbates to Foods by Food Category (18)**

<table>
<thead>
<tr>
<th>Food category</th>
<th>Ascorbic acid</th>
<th>Ascorbyl palmitate</th>
<th>Erythorbic acid (isoascorbic acid)</th>
<th>Sodium ascorbate</th>
<th>Sodium erythorbate (sodium isoascorbate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baked goods, baking mixes</td>
<td>0.028</td>
<td></td>
<td></td>
<td>0.094</td>
<td></td>
</tr>
<tr>
<td>Breakfast cereals</td>
<td>0.013</td>
<td></td>
<td></td>
<td>0.093</td>
<td></td>
</tr>
<tr>
<td>Fats and oils</td>
<td></td>
<td>0.010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milk products</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td>0.030</td>
<td></td>
</tr>
<tr>
<td>Frozen dairy desserts, mixes</td>
<td>0.016</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Processed fruits, juices, drinks</td>
<td>0.032</td>
<td></td>
<td></td>
<td></td>
<td>0.120</td>
</tr>
<tr>
<td>Fruit ices, water ices</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meat products</td>
<td>0.046</td>
<td></td>
<td></td>
<td>0.033</td>
<td></td>
</tr>
<tr>
<td>Poultry products</td>
<td>0.046</td>
<td></td>
<td></td>
<td>0.036</td>
<td>0.012</td>
</tr>
<tr>
<td>Fish products</td>
<td>0.010</td>
<td></td>
<td></td>
<td></td>
<td>0.036</td>
</tr>
<tr>
<td>Processed vegetables, juices</td>
<td>0.016</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condiments, relishes, salt substitutes</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft candy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Jams, jellies, sweet spreads</td>
<td>0.127</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweet sauces, toppings, syrups</td>
<td>0.196</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gelatins, puddings, fillings</td>
<td>0.024</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soups, soup mixes</td>
<td>0.018</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beverages, nonalcoholic</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Beverages, alcoholic</td>
<td>0.012</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Gravies</td>
<td>0.194</td>
<td></td>
<td></td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>Dairy products analogs</td>
<td></td>
<td></td>
<td></td>
<td>0.112</td>
<td></td>
</tr>
<tr>
<td>Hard candy</td>
<td>0.248</td>
<td></td>
<td></td>
<td>0.120</td>
<td></td>
</tr>
<tr>
<td>Instant coffee and tea</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baby formulas</td>
<td>0.012</td>
<td></td>
<td></td>
<td></td>
<td>0.016</td>
</tr>
<tr>
<td>Baby processed fruit</td>
<td>0.048</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baby puddings</td>
<td>0.047</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baby combination dinners</td>
<td>0.040</td>
<td></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 ascorbates 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 18.
<table>
<thead>
<tr>
<th>Age group</th>
<th>Ascorbic acid (mg)</th>
<th>Ascorbyl palmitate (mg)</th>
<th>Erythorbic acid (isoascorbic acid) (mg)</th>
<th>Sodium ascorbate (mg)</th>
<th>Sodium erythorbate (sodium isoascorbate) (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 mo</td>
<td>90</td>
<td>0.1</td>
<td>0.7</td>
<td>66</td>
<td>0.5</td>
</tr>
<tr>
<td>6-11 mo</td>
<td>136</td>
<td>0.3</td>
<td>12.6</td>
<td>146</td>
<td>8.7</td>
</tr>
<tr>
<td>12-23 mo</td>
<td>130</td>
<td>0.6</td>
<td>19.7</td>
<td>231</td>
<td>12.7</td>
</tr>
<tr>
<td>2-65+ yr</td>
<td>213</td>
<td>1.8</td>
<td>49.0</td>
<td>338</td>
<td>31.6</td>
</tr>
</tbody>
</table>
Two alternative approaches to estimating intakes of ascorbates suggest that actual intakes of added ascorbic acid and ascorbates are considerably less than those listed in Table III. One method of estimating per capita daily intakes is based on annual poundage data provided in the NRC report (18) concerning ascorbates used as food ingredients in 1970 (Table IV). Such disappearance data are likely to be somewhat in excess of per capita consumption. Nevertheless, the values are only a fraction of those presented as possible average daily intakes in Table III. For example, quantities of ascorbic acid and sodium ascorbate used by industry were sufficient to provide for 25 and 9 mg, respectively, per capita daily; for erythorbic acid and sodium erythorbate, corresponding figures were 6 and 7 mg per capita daily. No annual poundage or other data on food uses of calcium ascorbate were included with the NRC report.

A second approach to estimating consumption is the analysis of results of various surveys of vitamin C intake. These surveys concern intakes of vitamin C from all sources (naturally present in foods, added to foods, consumed in supplements). Table V presents data from the Health and Nutrition Examination Survey (HANES) (21) concerning intake of vitamin C by individuals grouped on the basis of age and sex. It may be seen that mean intakes ranged from 67 to 117 mg per day. Data from the Ten-State Nutrition Survey (22) and from a USDA Survey (23) generally yielded slightly lower mean values for the various age groups. Because intakes reported in these surveys refer to all dietary sources of vitamin C, it seems unlikely that amounts of vitamin C added to foods in processing could account for the intakes noted in Table III. The Select Committee regards the per capita daily intakes of 25 mg ascorbic acid, 9 mg sodium ascorbate, 6 mg erythorbic acid and 7 mg sodium erythorbate as reasonable estimates of intakes of these substances added to foods.

The several surveys have also provided data on the upper percentiles of intake of vitamin C from all sources. Table VI indicates that 25 to 39 percent of individuals in various age groups received more than 99 mg of vitamin C on the day of survey (24). Twelve to 19 percent of individuals in the various age groups received more than 149 mg of vitamin C on the day of survey. For intakes greater than 99 mg by individuals more than 2 years of age, data from the Ten-State Survey (22) are generally similar. A lesser percentage of individuals in the Ten-State Survey than in the HANES (24) received more than 149 mg of vitamin C on the day of survey.
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascorbic acid</td>
<td>2.4</td>
<td>1,900,000</td>
<td>25</td>
</tr>
<tr>
<td>Ascorbyl palmitate</td>
<td>2.0</td>
<td>50</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Erythorbic acid</td>
<td>0.3</td>
<td>420,000</td>
<td>6</td>
</tr>
<tr>
<td>Sodium ascorbate</td>
<td>3.3</td>
<td>680,000</td>
<td>9</td>
</tr>
<tr>
<td>Sodium erythorbate</td>
<td>2.4</td>
<td>500,000</td>
<td>7</td>
</tr>
</tbody>
</table>

\(a^{\text{Based only on the reports from those respondents to the National Research Council (NRC) survey who submitted information for both 1960 and 1970.}}\)

\(b^{\text{Total usage is based on the sum of kilograms used in foods reported by NRC and the Flavor and Extract Manufacturers' Association recalculated to 100 percent from survey data that the NRC subcommittee estimated to represent about 60 percent of the actual usage.}}\)

\(c^{\text{Based on the quantities indicated in Column 3 and a United States population of 205 million.}}\)
### TABLE V

**Mean Intakes* of Vitamin C by Various Age Groups in HANES (21)**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Vitamin C Intake (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Both sexes</td>
</tr>
<tr>
<td>1</td>
<td>67</td>
</tr>
<tr>
<td>2-3</td>
<td>78</td>
</tr>
<tr>
<td>4-5</td>
<td>82</td>
</tr>
<tr>
<td>6-7</td>
<td>79</td>
</tr>
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<td>8-9</td>
<td>81</td>
</tr>
<tr>
<td>10-11</td>
<td>89</td>
</tr>
<tr>
<td>12-14</td>
<td>89</td>
</tr>
<tr>
<td>15-17</td>
<td>101</td>
</tr>
<tr>
<td>18-19</td>
<td>117</td>
</tr>
<tr>
<td>20-24</td>
<td>108</td>
</tr>
<tr>
<td>25-34</td>
<td>90</td>
</tr>
<tr>
<td>35-44</td>
<td>83</td>
</tr>
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<tr>
<td>55-64</td>
<td>96</td>
</tr>
<tr>
<td>65+</td>
<td>88</td>
</tr>
</tbody>
</table>

*From all sources naturally present in and added to foods.

### TABLE VI

**Intake of Vitamin C on Day of HANES (24)**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Intake &gt;99 mg</th>
<th>Intake &gt;149 mg</th>
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<tbody>
<tr>
<td>1-6*</td>
<td>25</td>
<td>12</td>
</tr>
<tr>
<td>18-45</td>
<td>30</td>
<td>17</td>
</tr>
<tr>
<td>&gt;60</td>
<td>39</td>
<td>19</td>
</tr>
</tbody>
</table>

*The designation 1-6 refers to all individuals who have reached 1 year of age and not yet reached their 6th birthday.
IV. BIOLOGICAL STUDIES

Occurrence and essentiality in animals and man

King (25) noted that ascorbic acid (vitamin C) is present in and appears to be essential for the normal functioning of all cellular units in higher plants and animals, including subcellular organelles such as ribosomes and mitochondria. Among animals studied thus far, only man, other primates, guinea pigs, and a few other animal species are dependent on dietary sources of the vitamin. Most animals can synthesize it from glucose.

A severe deficiency of ascorbic acid causes scurvy. This is characterized by lassitude, joint tenderness, swollen and inflamed gums, anemia, capillary hemorrhages, failure of wounds to heal, and failure of the cartilage, bone, and dentine to develop normally (26). The connective tissue defects resulting from insufficient vitamin C are caused by impaired synthesis and metabolism of collagen (27). Ascorbic acid is necessary for the activation of proline hydroxylase, an enzyme required in the formation of hydroxyproline in the collagen polypeptide chains. This is an essential step for the conversion of procollagen to fibrous collagen.

Other biochemical roles of ascorbic acid are related to its properties as a reducing agent, the promotion of iron absorption, the catabolism of cholesterol to bile acids, and the transfer of sulfate groups (28-30). Ascorbic acid also participates in other hydroxylation reactions such as the conversion of p-hydroxyphenylpyruvic acid to homogentisic acid in tyrosine metabolism, and the hydroxylation of tryptophan, dopamine, steroids and possibly lysine (31, 32). Thus the biochemical changes resulting from a deficiency of vitamin C are complex and involve several different metabolic systems.

Absorption, metabolism and excretion

Ascorbic acid

Ingested ascorbic acid is rapidly absorbed from the alimentary tract (25). The biological half-life of ascorbic acid in man, as determined in three patients, is approximately 16 days (33). A recent study (34) indicated that the half-life of ascorbic acid in the normal adult male decreases with increasing total turnover, approaching about 10 days at a total turnover of 70 mg per day.

The total body store of ascorbic acid in a healthy human adult is estimated to be about 1.5 g, but this is markedly decreased when the level of intake is reduced for some time (35, 36). If the body pool falls below 300 mg, clinical signs of scurvy appear (37). In addition, the tissue distribution of ascorbic acid is not uniform. The highest concentrations occur in the adrenal and pituitary glands, followed by the eye lens, liver,
spleen, brain, pancreas, kidney, and heart muscle. The plasma concentration is considerably lower, and it does not directly reflect the tissue concentrations or the degree of tissue saturation with the vitamin. However, in a recent study of steady state kinetics, Kallner et al. (34) showed that, in healthy adult men, the plasma steady state concentration of ascorbic acid correlates with total daily turnover and that, even with low dosages (30 mg per day) some ascorbic acid is excreted unchanged in the urine. In general, the pattern of tissue distribution of ascorbic acid in man is similar to that found in other species, e.g., rat and guinea pig (38). It is believed that the renal reabsorption of ascorbic acid (39) and the uptake of the vitamin by tissues are stereospecific energy-requiring active transport processes (40).

Recently, Siliprandi et al. (41) reported that in the brush border vesicles of guinea pig small intestine, L-ascorbate transport is Na⁺-dependent and electroneutral; that the L-ascorbate transporter has the kinetic characteristics of a mobile carrier; that D-isoascorbate competes with L-ascorbate for the transport system; and that L-ascorbate uptake by brush border vesicles of the small intestine is heterologously inhibited by D-glucose, an effect of unknown physiological significance. In addition, preliminary experiments indicated that the uptake of L-ascorbate into membrane vesicles from the renal cortex of guinea pigs is also activated by Na⁺. The possible influence of D-isoascorbate on renal tubular reabsorption of L-ascorbate was not addressed.

Man requires slightly more than 1 mg of ascorbic acid per kg body weight per day to maintain a body pool of 20 mg per kg. L-ascorbic acid-1-¹⁴C was administered intravenously to three patients in single doses of 23.9 to 37.2 μCi (33). During the following 10 days an average of 42 percent of the administered dose appeared in the urine, one percent in the feces, and no ¹⁴C was detected in the respiratory CO₂. About 25 percent of the total urinary label was present as ascorbic acid, a smaller proportion as 2,3-diketogulonic acid, and most of the remainder as oxalate. Other urinary metabolites have been identified in man, including ascorbate-2-sulfate (42). Man does not catabolize ascorbic acid to CO₂ to any appreciable extent (33, 43, 44), but the monkey does metabolize vitamin C and ascorbate-2-sulfate to CO₂ when either is given orally (42). In a metabolic study of a normal human adult male receiving a diet moderately low in vitamin C, a single dose test supplement of 50 mg labeled ascorbic acid was given by mouth (45). Oxalate formation and urinary excretion of ascorbic acid accounted for about half the total ascorbic acid turnover. The authors noted that the remainder of the labeled ascorbic acid was catabolized via pathways compatible with the production of CO₂ from the number 1 carbon. The unusually large portion of ascorbic acid apparently converted to CO₂ in this study may have been due to decomposition of ascorbic acid in the aqueous solutions used (42). A study using ³H-labeled ascorbic acid given to a human subject showed that the label does not enter
the body water pool, but is excreted as organic-bound tritium (44). This
tends to confirm other data showing no conversion of labeled ascorbate
to CO₂.

**Erythorbic acid**

Erythorbic acid is well absorbed, but not as rapidly as L-ascorbic acid (46). It distributes into tissues, although it is taken up less efficiently than L-ascorbic acid by white blood cells, brain, adrenal glands, and the eye (47, 48). Hughes and Hurley (46) found that L-ascorbic acid is absorbed more efficiently than erythorbic acid in guinea pigs. At equivalent doses (3 mg per kg body weight) erythorbic acid was not taken up by tissues such as the adrenal gland. These workers found no evidence of any conversion of erythorbic acid to L-ascorbic acid in vivo.

Renal excretion of erythorbic acid is more rapid than that of L-ascorbic acid, apparently because it is not reabsorbed after glomerular filtration; L-ascorbic acid is reabsorbed by a specific transport system, characterized by a saturable Tₘ (tubular maximum), resembling the specialized system for glucose reabsorption (39). As a consequence of the rapid renal excretion of erythorbic acid, there is a short half-life of erythorbic acid in plasma, estimated to be about 30 minutes in dogs (49).

Other workers studied the renal excretion of erythorbic acid in five normal human subjects (50). They found that 300 mg of erythorbic acid given orally did not alter the rate of renal excretion of L-ascorbic acid in 4 hours. Wang et al. (51) found that erythorbic acid was excreted to a greater extent than L-ascorbic acid in man; the erythorbic acid is filtered but not appreciably reabsorbed by the kidney.

Erythorbic acid is as effective as vitamin C as an antioxidant, but it has only about one-twentieth the antiscorbatic activity of L-ascorbic acid when fed to guinea pigs (52-54). Erythorbic acid given in daily oral doses of 10 mg replaced the antiscorbatic activity of 1 mg L-ascorbic acid, but did not support weight gain as well as in animals receiving 1 mg ascorbic acid daily (53). Analysis of the hydroxyproline content of the skin of guinea pigs fed a scorbutigenic diet supplemented with 10 mg daily of erythorbic acid for 115 days indicated no difference from the values obtained in guinea pigs receiving vitamin C (53). One laboratory found that guinea pigs fed 250 mg of erythorbic acid per day still developed scurvy, but the isomer did help suboptimal amounts (0.3 mg per day) of L-ascorbic acid to prevent scurvy when given with the vitamin in doses of 10 to 100 mg per day (55).

Pelletier and Godin (47) found that it required 40 mg of erythorbic acid per day compared with 2 mg of L-ascorbic acid to prevent scorbutic symptoms in the guinea pig. They also found that animals given erythorbic acid had a lower concentration of ascorbic acid in their tissues, such as
the adrenal glands, and concluded that erythorbic acid had no sparing action on ascorbic acid. In additional studies, these authors found that the turnover rate of erythorbic acid was much faster than for ascorbic acid in all the tissues examined, and that erythorbic acid caused an increase in the rate of turnover of ascorbic acid in the tissues (48). The reduced antiscorbutic activity of erythorbic acid is presumably explained by its reduced absorption, less efficient tissue uptake, and its rapid metabolism and renal excretion.

Studies on the transport of erythorbic acid into the aqueous humor of guinea pig eyes indicated that the uptake process was the same for both diastereoisomers, but the affinity for erythorbic acid was about one-fifth that for L-ascorbic acid (56). These results lead to the conclusion that the two isomers should compete in the uptake process. Other in vivo and in vitro studies in rabbits have shown a marked specificity for the transport of L-ascorbic acid into the central nervous system, and inhibition of this uptake process by erythorbic acid and by glucoascorbic acid (40). The latter two isomers are not transported as effectively as L-ascorbic acid into the choroid plexus in vitro or into the cerebrospinal fluid in vivo.

No reports of the absorption, distribution, and excretion of calcium ascorbate, sodium ascorbate, and ascorbyl palmitate were available to the Select Committee, and studies of biological effects of these compounds were limited to one long-term study of ascorbyl palmitate in rats and the teratogenicity and mutagenicity tests described in this report. However, because ingested ascorbic acid forms both calcium and sodium ascorbates in the gastrointestinal tract and ascorbyl palmitate would yield ascorbic acid during digestion, the absorption and metabolism of their ascorbyl moiety would be expected to be essentially the same as for ascorbic acid.

Interactions of L-ascorbic acid and erythorbic acid

Several studies have examined the effect of erythorbic acid on L-ascorbic acid uptake and disposition in guinea pigs. Hornig et al. (57) fed guinea pigs a basal diet supplemented with 20 mg of L-ascorbic acid per day and various levels (0, 20, 50, 100, or 400 mg per day) of erythorbic acid for 3 days. A tracer dose of $^{14}$C-labeled L-ascorbic acid was then given and the radioactivity determined in the tissues 6 hours later. In the animals receiving 50 mg or more erythorbic acid there was a significant reduction in uptake of ascorbic acid in the pituitary, adrenals, lungs, kidneys, testes, eyes, and pancreas, and at higher erythorbic acid levels, a further decrease in the uptake of the labeled ascorbic acid in these tissues. The authors concluded that erythorbic acid decreased the size of the ascorbic acid pool and the uptake of vitamin C by tissues by about 50 percent. More recently, Hornig and Weiser (58) supplemented the diets of vitamin C-depleted guinea pigs with 50 mg erythorbic acid per kg body weight per day for 16 days. They found accelerated catabolism of a tracer dose of labeled L-ascorbic acid
compared to animals supplemented with ascorbic acid (5 mg per kg body weight per day). This effect was not normalized by additional ascorbic acid supplementation. They concluded that the bioavailability of vitamin C was reduced to approximately 50 percent by erythorbic acid.

As previously noted, in studies on the relative uptake of erythorbic acid and L-ascorbic acid in the guinea pig eye, other workers found similar saturation kinetics for both isomers but the affinity of L-ascorbic acid for transport was 4 to 5 times greater than that of erythorbic acid (56). Apparently the transport mechanism is similar for both isomers, and their competitive behavior is proportional to their relative concentrations and affinities.

Goldman et al. (59) studied the influence of L-ascorbic acid, D-isoascorbic acid (erythorbic acid) or combinations of these on growth, serum alkaline phosphatase levels, wound healing, and developmental tooth structure in young female guinea pigs fed scorbutigenic diets. Daily supplements of 100 mg erythorbic acid for 7 weeks resulted in normal growth rates, phosphatase levels, tooth development, and wound healing. Addition of 0.5 or 5 mg L-ascorbic acid to the supplement did not improve rates of weight gain or collagen deposition in wounds. Signs of scurvy appeared more rapidly after withdrawal of erythorbic acid following prolonged administration than after withdrawal of an erythorbic acid—L-ascorbic acid mixture. The authors concluded that erythorbic acid is weakly antiscorbutic and has no appreciable competitive effect with L-ascorbic acid on the basis of the above-mentioned biological parameters.

Supplements of 50 or 100 mg of erythorbic acid per day to a vitamin C-deficient diet given to two young healthy adult male subjects partially depleted of ascorbic acid produced no repletion of blood white cell ascorbic acid levels or elevation of plasma ascorbic acid concentration, and a loading dose of 300 mg of erythorbic acid had no effect on white cell ascorbic acid concentrations in these subjects (60).

**Acute toxicity**

Tables VII and VIII list data on the acute and subchronic toxicity of excessive amounts of ascorbic acid in different animal species. In addition, acute toxicity data on erythorbic acid are shown in Table VII.

In mice, rats, and guinea pigs, the oral LD\textsubscript{50} of sodium ascorbate has been reported to be greater than 5.0 g per kg. Intravenously its LD\textsubscript{50} was greater than 1.0 g per kg for mice and rats; and greater than 0.5 g per kg for guinea pigs (67).

For ascorbic acid neutralized with sodium carbonate and administered intravenously, the LD\textsubscript{100} was between 6.4 and 7.3 g per kg in rabbits. No toxic effects were apparent at the level of 5.3 g per kg, but at 6.4 g per kg tremors in the legs were noted (68).
TABLE VII
Acute Toxicity of Ascorbic Acid and Erythorbic Acid (LD₅₀ in 24 Hours)

<table>
<thead>
<tr>
<th>Species</th>
<th>Doses in g per kg</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral</td>
<td>S.C.</td>
</tr>
<tr>
<td>Ascorbic Acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouse</td>
<td>8.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Rat</td>
<td>&gt;5.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>&gt;5.0</td>
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<tr>
<td>Rabbit</td>
<td>&gt;2.0</td>
<td>&gt;1.0</td>
</tr>
<tr>
<td>Cat</td>
<td>&gt;1.0</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>Dog</td>
<td>&gt;5.0</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Erythorbic Acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouse</td>
<td>8.3</td>
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</tr>
<tr>
<td>Rat</td>
<td>18.0</td>
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</tbody>
</table>

¹Bächtold, H.P., unpublished data, referred to in reference 61.
<table>
<thead>
<tr>
<th>Species</th>
<th>Oral Dose (mg per kg per day)</th>
<th>S.C. Dose (mg per kg per day)</th>
<th>T.V. Dose (mg per kg per day)</th>
<th>Duration (days)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>&gt;6500</td>
<td>&gt;600</td>
<td>&gt;8900</td>
<td>10</td>
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</tr>
<tr>
<td>Rat</td>
<td>&gt;6500</td>
<td>&gt;600</td>
<td>&gt;8900</td>
<td>10</td>
<td>61b</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>500</td>
<td>500</td>
<td>100</td>
<td>6</td>
<td>61c</td>
</tr>
<tr>
<td>Rabbit</td>
<td>&gt;500</td>
<td>&gt;500</td>
<td>&gt;2000</td>
<td>3</td>
<td>61c</td>
</tr>
<tr>
<td>Cat</td>
<td>100</td>
<td>100</td>
<td>&gt;2000</td>
<td>3</td>
<td>61c</td>
</tr>
<tr>
<td>Dog</td>
<td>100</td>
<td>100</td>
<td>&gt;2000</td>
<td>3</td>
<td>61c</td>
</tr>
</tbody>
</table>

*Modified from Körner and Weber (61).*

*Bitchold, H. P., unpublished data referred to in reference 61.*

*DeMole, V., unpublished data referred to in reference 61.*
Short-term studies (animals)

Since pure ascorbic acid became available in 1934, many studies have been made to determine the effects of administering large amounts of the vitamin to animals. No harmful effects were observed in rats following the oral administration of 6.5 g ascorbic acid per kg of body weight daily over a period of 10 weeks (69). On the other hand, daily doses of 27.3 g per kg were toxic; the mortality rate rose to 77 percent within 4 weeks. The investigators concluded that the maximum nontoxic dose in the rat was about 10 g per kg. They related this to man by noting that on this basis a daily human intake of 1 g affords a safety factor of 700.

Four groups of young rats received ascorbic acid added to the diet at the levels 0, 1, 5, and 10 percent (estimated to be 1.0, 5.0, and 10.0 g ascorbic acid per kg per day) (70). Weight gain was slightly reduced in the group receiving 1 percent and increasingly reduced in the other two groups. A laxative effect was noted in the group receiving 10 percent ascorbic acid, and two of the six rats in this group died.

Three groups of female guinea pigs were fed ascorbic acid at levels of 4, 10, or 100 mg per kg body weight beginning at 14 days of age and continuing until they had produced and weaned three litters (71). The female offspring were fed the same level of ascorbic acid as the parents. It was reported that at the lowest dietary ascorbic acid level, initiation and maintenance of pregnancy were less successful than in animals given larger supplements of ascorbic acid, and the offspring of parent animals fed the highest level (100 mg per kg) had a reduced survival rate.

There was a highly significant increase in mortality in chicks given a diet containing 0.5 percent ascorbic acid (approximately 625 mg per kg body weight) during the first month after hatching (72). Lang (63) reported that in rats the daily intake of ascorbic acid tolerated without apparent harm for 6 weeks was at least 10 g per kg body weight. Studies with guinea pigs led to the same value. In dogs, there were no adverse effects noted from the intravenous administration of 1.0 g per kg of sodium ascorbate over a 20-day period. Histologically, the livers and kidneys were normal (68).

Short-term studies (humans)

In 1952 one woman and three men received a 1.0 g daily supplement of ascorbic acid in three divided doses with meals for 3 months (73). After the first 5 days there was no further apparent change in the average concentrations of the vitamin in the blood serum, white cells, and urine, and the 7-hour tolerance curves for ascorbic acid in the serum did not change during the remainder of the test period. The serum and white cell concentrations of ascorbic acid before dosage started were high enough to
indicate that the subjects had been receiving adequate amounts of the vita-
min. It was concluded that no harmful effects had occurred during the 3-
month test period.

Long-term studies

Few investigations have been reported on the effects of ingesting large amounts of ascorbates during virtually an entire lifetime or through more than one generation. In an extensive toxicity investigation reviewed by Köörner and Weber (61), three groups of 26 rats of both sexes were fed a balanced stock ration for approximately 2 years. Enough ascorbic acid was added to the test diet to assure intakes for each rat of 1.0, 1.5, or 2.0 g per kg body weight per day. The controls were given the same diet without added ascorbic acid. There was no effect attributable to the ascorbic acid on the weight, mortality, general physical condition, blood and urine chemistry, liver and kidney function tests, or macro- and micropathological appearance of the various organs and tissues examined. Reproductive tests were not conducted.

Rats fed ascorbyl palmitate for 2 years at the level of 0.25 percent in the diet (estimated to be about 125 mg per kg per day, equivalent to about 53 mg ascorbic acid per kg per day) showed no harmful effects (74). Rats fed erythorbic acid for 6 months at a concentration of 1 percent of the diet showed no difference from controls in rate of weight gain, and, after 2 years at 1 percent of the diet, no pathologic lesions attributable to the erythorbic acid (75). Four beagles received a total of 1 g erythorbic acid daily by oral administration for 240 days (62). Four other beagles received oral doses of 5 g erythorbic acid daily for 50 days, then 7.5 g daily for another 190 days. No signs of toxicity were observed in either group during the experimental period. Body weights, growth, and hematograms remained normal. No gross or microscopic pathologic changes were found in any of the dogs.

Pregnancy and fetal health

A review of studies of tolerance to high doses of ascorbic acid by Köörner and Weber (61) included information from reports on the reproductive success of guinea pigs receiving high dietary levels of the vitamin. For example, paired test males and females, given a diet containing 0.5 percent ascorbic acid, consumed about 500 mg per kg per day. These animals did not differ from the controls in the number and size of the litters or in any other aspect of fertility.

Frohberg et al. (76) gave pregnant rats daily oral doses of 150, 250, 500, and 1000 mg ascorbic acid per kg in a first trial from day 6 to day 15 of pregnancy and in a second trial from day 0 postconception to day 21 post-
partum. Also, mice were given daily oral doses of 250, 500, or 1000 mg
per kg from day 6 to day 15 of pregnancy. There were no indications of adult-toxic, teratogenic, or fetotoxic effects. There was no apparent effect on the embryonic and postpartum development of the young or on breeding behavior, pregnancy, parturition, and lactation capacity of the mother animals.

Rivers (77) reported the reproductive performance of guinea pigs fed 1.5, 4.0, or 100.0 mg ascorbic acid per kg body weight over three generations. Animals fed the highest level of ascorbic acid produced the most litters and had the fewest abortions, but there were no differences among the groups in number of newborns or viable young. Tissues of offspring whose dams were fed 1.5 or 4.0 mg ascorbic acid per kg were below saturation and, in some cases, below maternal values, suggesting that the fetus suffers before the mother when dietary ascorbic acid is limited and that the requirement for ascorbic acid during pregnancy has been underestimated.

Experiences with large amounts intended for therapeutic purposes

Many studies have been reported in which the administration of large amounts of ascorbates has been tested as a therapeutic procedure. In a number of instances, the information gained has been useful in the evaluation of the safety of ascorbic acid added to food. For example, in 1971, Hoffer (78) reported that, starting in 1953, total doses of 3 to 30 g (about 50 to 500 mg per kg) ascorbic acid had been given daily to about 1000 patients, most of whom were schizophrenic. He did not observe any instances of kidney stone formation, miscarriage, excessive dehydration, or any other "serious toxicity." Diarrhea was the most notable side-effect, and it was controlled by reducing the dosage by 1 or 2 g.

In a controlled blind study, 40 male chronic psychiatric patients were given either 1 g ascorbic acid or a placebo in single daily doses by mouth for 3 weeks (79). Initially some of the patients had signs of scurvy, which disappeared with the administration of the vitamin. No harmful effects of consuming 1 g ascorbic acid daily were noted.

VanderKamp (80) administered ascorbic acid in divided doses to eight normal adults and ten chronic schizophrenic patients. The former received an average total daily dose of 4 g and the latter 40 g. Other schizophrenic patients received 36 to 48 g daily for therapeutic purposes. The author did not report the duration of the ascorbic acid treatment, which is assumed to have been several weeks. No adverse effects of the vitamin were reported in any of the normal test subjects or patients.

In a study of the effects of ascorbic acid on burns, 62 cases were reported (81). The vitamin was given in amounts ranging from 300 to 2000 mg daily in divided doses. At no time were deleterious effects from
the vitamin observed. The authors concluded that ascorbic acid alleviated pain of minor burns, expedited healing, shortened time interval to skin grafting, and aided in deterring accumulation of toxic protein metabolites.

As a nonspecific treatment for lenticular opacities, a male patient took 4 g of ascorbic acid per day (82). After 13 years, he had not experienced any hyperoxaluria or nephrolithiasis or any other disorder attributable to the ascorbic acid. His physician reported that none of his many other patients who had taken large amounts of vitamin C showed signs of injury.

In uncontrolled clinical studies by Greenwood (83) of over 500 adults with early intervertebral disc lesions with lumbosacral strain or sciatic nerve involvement, ascorbic acid was prescribed in daily dosages of 750 to 1000 mg. This was continued for a few months or years. Apparently there were no adverse effects attributable to the large amounts of ascorbic acid. The author concluded that vitamin C is beneficial in the treatment of disc conditions.

The focus of public attention on ascorbic acid and the common cold around 1970 was accompanied by a number of clinical studies some of which furnished considerable information on the safety aspects of ascorbates as dietary supplements or as additives to food. Pauling (84) claimed that "an increased intake of ascorbic acid 10 to 100 times the daily allowance recommended by the Food and Nutrition Board leads to improvement in general health and to increased resistance to infectious disease, including the common cold." For average weight adults, this amounts to 450 to 4500 mg per person. The literature cited by Pauling (84) indicated no evidence of injury at such levels or severalfold higher.

Each of 407 test subjects ingested 1 g per day of a mixed ascorbic acid, sodium ascorbate preparation for at least 2 months (85). This was in addition to vitamin C in their regular diets. When subjects first detected signs or symptoms of a cold, they increased their intake of the ascorbic acid, sodium ascorbate mixture to 4 g per day. No unfavorable effects were noted in any of the subjects. A study by Coulehan and associates (86) of the effects of large amounts of ascorbic acid on upper respiratory illness in Navaho children revealed a low but increased incidence of "abdominal symptoms" in the subjects taking ascorbic acid. The ascorbate dosage was 1.0 g per child daily in divided doses for 17 weeks. No other adverse effects were noted. Other investigators in comparable investigations and for the same purposes, but using adult subjects, have not reported the occurrence of adverse effects. In such studies the dosages of ascorbate generally ranged from 0.5 to 2.0 g per person per day (87-91).
Considerable attention has been given to possible interrelationships between ascorbic acid and the pathogenesis of atherosclerosis (29). In none of the studies, involving either animals (92, 93) or human subjects (94, 95), have the large amounts of administered ascorbic acid resulted in signs of toxicity.

Dependency on excess ascorbate

It has been reported from several different laboratories that the extended ingestion of large amounts of ascorbic acid causes a dependency on larger levels of intake (96). This has been briefly reviewed and supported by Rhead and Schrauzer (96), but denied by Hornig et al. (97). Gordonoff (98) gave guinea pigs 500 mg ascorbic acid per animal daily for 4 weeks. These animals and a control group that had been fed the same basal diet were changed to an ascorbate-free diet. The animals that had received an excess of the vitamin had an average survival of 24.8 days; the controls survived 36.8 days. Hornig and his associates (97) reported that the rate of catabolism of 1-14C-labeled ascorbic acid was unchanged in guinea pigs fed diets for 3 weeks that contained up to 25 g of ascorbic acid per kg diet. However, Sorensen et al. (99) found that the growth rate of male guinea pigs was clearly impaired when the diet contained 86 g ascorbic acid per kg during a period of 275 days (estimated to be about 6 g per kg body weight per day after 150 days at this level of intake). The controls received 2 g per kg of diet (estimated to be about 100 mg per kg body weight after 150 days at this level of intake). The catabolism of labeled ascorbic acid was significantly increased during the high intake of the vitamin. This continued after the intake of ascorbic acid was decreased to 3 mg per kg of diet (estimated to be about 0.2 mg per kg body weight per day) for 68 days and when the diet was free from the vitamin for 44 days. Thus, the animals fed large amounts of ascorbic acid were depleted of the vitamin more rapidly than the controls.

As reported by Schrauzer and Rhead (100), continuous ascorbate overdosage in human subjects leads to systemic conditioning primarily characterized by the accelerated metabolism and excretion of the vitamin. Also, there is a decrease in the ability of rabbits as well as humans to withstand conditions of limited oxygen supply (101). Human subjects receiving 3 g of ascorbic acid daily for 9 days had lowered resistance to low oxygen levels, but those receiving 2 g per day apparently were not affected.

Pregnant guinea pigs were given diets containing 0.5 percent or 0.05 percent ascorbic acid (estimated to be about 200 or 20 mg per kg body weight per day) (102, 103). Pups were weaned to an ascorbic acid-free diet on day 10. Signs of scurvy and death occurred significantly earlier in the pups from mothers fed the 0.5 percent ascorbic acid diet.
The suggestion of Cochrane (104) that scurvy in two infants may have resulted from excessive maternal intakes of ascorbic acid (estimated at 400 mg per day) during pregnancy was cited as an important consideration in a 1975 review of the safety of high doses of ascorbic acid (105).

The validity of the dependency hypothesis was strengthened by the finding of Peterson et al. (106) that the activity of several enzymes in guinea pigs is markedly decreased when the animals are fed a diet containing 84 g ascorbic acid per kg feed. Also, it was supported by a study of the concentration of ascorbic acid in the blood serum of 17 young adult students who ingested 1 to 3 g of ascorbic acid daily over periods of 3 to 36 months (96). After 10 days on a "standardized" supplemental daily intake of 2.0 g, the mean serum ascorbic acid concentration was 1.45 ± 0.55 mg per 100 ml as compared with 1.20 ± 0.55 mg per 100 ml in 16 normal controls not receiving supplemental ascorbic acid. When the control group ingested 2.0 g ascorbic acid per person daily for 8 days, the mean serum levels were 2.75 ± 0.65 mg per 100 ml. The findings suggest that metabolic adjustments occur and the concentration of ascorbic acid tends to remain only slightly higher than normal after ascorbate has been ingested in large amounts over a long time.

**Oxalate excretion and stones**

Considerable attention has been given to calcium oxalate nephrolithiasis as a possible consequence of prolonged ingestion of excessive amounts of ascorbic acid. Hellman and Burns (33) gave three patients single intravenous injections of $^{14}$C-L-ascorbic acid in doses that varied from 23 to 37 mg (23 to 37 μCi). An average of 44 percent of the total radiocarbon excreted in the urine was recovered as oxalate. Only a small fraction of the injected radiocarbon was recovered in respiratory CO$_2$ and feces. Lamden and Chrystowski (107) studied the influence in human adult males of different doses of orally administered ascorbic acid on 24-hour urinary oxalate excretion. Less than 4 g per day ascorbic acid produced negligible increases while, at levels of 4 and 9 g ascorbic acid per day, the average increases in total oxalate excretion were 12 and 68 mg, respectively.

Guinea pigs given 250 mg of the vitamin daily excreted about 3.5 mg of oxalate per day, which was similar to that of the controls (108). In man, 35 to 50 percent of the urinary oxalate appears to be derived from ingested ascorbic acid, but urinary oxalate represents only 20 to 40 percent of the metabolic turnover of ascorbic acid (109,110). As reported by Hagler and Herman (109), most patients with oxalate nephrolithiasis have no primary disorder of oxalate metabolism and excrete normal amounts of oxalate in the urine.
Occasional exceptions to this pattern of ascorbic acid metabolism are found. For example, Briggs et al. (111) described an apparently healthy young man whose daily urinary oxalate excretion before supplementation with ascorbic acid was approximately 58 mg. After he had ingested 4 g of ascorbic acid daily in 4 divided doses for 7 days, the 24-hour oxalate excretion rose to 622 mg. After a second course of the supplement for 4 days the amount of oxalate was 478 mg. In other subjects given the same test, the increase in excreted oxalate was about 12 mg. In a 9-year-old girl with oxalosis, the daily ingestion of 2 g of supplemental ascorbic acid for 5 days resulted in an increase in the already elevated oxalate excretion in the urine (61). Two healthy children and a girl with hypercalcemic urolithiasis received comparable supplements, but in no case was there a substantial increase in the excretion of oxalate. Some other instances of such aberrations have been reported, but they are rare.

It does not appear that the pattern of oxalate formation normally changes after a prolonged period of high ascorbic acid intake. Takiguchi et al. (112) observed no significant increase in the urinary oxalic acid in human adults following the daily ingestion of 1 to 2 g of ascorbic acid for 90 to 180 days.

Few data have been reported on oxalate formation from the salts of ascorbic acid. However, Fitzhugh and Nelson (74) investigated the tolerance of weanling rats to large amounts of ascorbyl palmitate and isoascorbil (erythorbil) palmitate. These substances were first incorporated in lard and then mixed with the basal diet. The palmitates were fed for 9 months at levels of 2 percent and 5 percent (estimated to be about 1.0 and 2.5 g per kg body weight per day [equivalent to about 424 and 1060 mg ascorbic acid per kg body weight per day, respectively] at the end of the test period). They were compared with one group given 1 percent erythorbic (isoascorbic) acid in the diet and a control group given no supplement. At the 5 percent level of ascorbyl or isoascorbil palmitate intake, there was a decrease in growth rate and, after 9 months, in two of eight animals that had received ascorbyl palmitate at the 5 percent dietary level, the urinary bladders were packed with oxalate stones. Among the remaining 58 rats in these studies there was an almost total absence of calcareous material and other changes.

**Interactions with metals**

Many reports suggest that substantial intakes of ascorbates generally diminish the toxicity of excesses of several heavy metals including lead, mercury, vanadium and cadmium (113-117). Holmes et al. (113) reported that high dietary levels of ascorbic acid offered protection against lead poisoning in factory workers and painters; and, in guinea pigs tested on a subacute schedule, subcutaneous injections of ascorbic acid every other day reduced the degree of plumism from oral doses of basic lead
carbonate (114). There is evidence that high intakes of ascorbate provide some protection against mercury poisoning (115), and ascorbic acid at 1 g per kg, when administered to mice prior to vanadium as NaVO₃ ⋅ H₂O interfered with the toxicity of the vanadium (116).

In studies with young Japanese quail, Fox (117) has shown that a supplement of 1 percent ascorbic acid in the diet partially or completely prevents the adverse effects of 75 ppm cadmium in the diet. She pointed out that many toxic effects of cadmium appear to be related to decreased intestinal absorption of certain indispensable trace inorganic elements. As she has stated, it is important to determine whether the adverse effects of cadmium exposure in man would be favorably affected by ascorbic acid.

The intricacy of the interactions with metals is illustrated in the study by Hill and Starcher (118) on the effects of ascorbic acid and erythorbic acid, at 0.1 percent in the diet, in reducing the uptake of copper in chicks. Both ascorbates decreased the growth of young chicks receiving a copper-deficient diet. This effect was alleviated by the provision of copper in the diet. The ascorbates had no effect on the depressed growth of chicks on iron-deficient and zinc-deficient diets. Such facts may have implications for the health of individuals ingesting large amounts of ascorbic acid if the dietary balance with respect to copper is unfavorable.

Further implications were presented in the study of interrelationships between dietary copper, iron and ascorbic acid in young pigs. Gipp and colleagues (119) showed that iron deficiency is the cause of the hypochromic anemia which occurs when the Cu:Fe ratio is highly elevated. Also, they have shown that the anemia follows a decrease in iron absorption and iron absorption is enhanced by ascorbic acid.

The general view that ascorbic acid promotes the absorption of iron has been strengthened by the clinical studies of Lee et al. (120). It was shown in human subjects that 50 mg of ascorbic acid administered with 200 mg of ferrous sulfate had little effect on iron absorption, but 1.0 g of ascorbic acid had a clear and substantial effect. More recently, Cook and Monsen (121) reported that in studies of 63 healthy adult men, nonheme iron absorption from a semisynthetic meal containing no meat but with ascorbic acid added over a range of 25 to 1000 mg increased in direct proportion to the amount of added ascorbic acid. At these extremes, the respective ratios of iron absorption with/without added ascorbic acid were 1.65 and 9.57. Although there appear to be no reports of excessive iron absorption attributable to large intakes of ascorbic acid, the authors suggested that in persons with disturbed regulation of iron absorption (as in idiopathic hemochromatosis, thalassemia major and sideroblastic anemia), large doses of ascorbic acid could result in excess iron absorption.
Relationships to vitamin B$_{12}$

It has been known since 1956 that, in ascorbate solutions, the cobalt in vitamin B$_{12}$ is reduced to monovalent cobalt, and that this, in effect, destroys the vitamin B$_{12}$ (122). Mayfield and Roehm (123) found that a large amount of ascorbic acid in the diet impaired the utilization of carotene and that the impairment was greater when the diet contained only small amounts of vitamin B$_{12}$.

It is doubtful that vitamin B$_{12}$ in food under ordinary conditions is substantially destroyed by large amounts of ascorbic acid, as reported by one group (122) and rather convincingly denied by another (124). However, some adverse relationship may exist as indicated further by the report that vitamin B$_{12}$ deficiency was observed in patients taking 1 g of ascorbic acid with each meal (3 g ascorbic acid per day) for 3 years or more (125).

Acid-base and electrolyte balance

In apparently normal adults the ingestion of 3 to 6 g ascorbic acid per day reportedly does not change the titratable acidity and the pH of the urine, and it is not considered to be very effective as an acidifier of the urinary tract (126). Also, in these amounts, it does not seem to affect the sodium balance adversely (61).

Blood coagulation and thrombocytes

Some studies have indicated that in normal subjects and in some disease states, large intakes of ascorbic acid induce thrombocytosis. Particular complications may arise if large amounts of ascorbic acid are ingested during prolonged treatment with Dicumarol® or heparin to control blood clotting (61,127). Unusual resistance to Dicumarol® was reported in a patient with acute thrombophlebitis who had been consuming approximately 16 g of ascorbic acid per day (128). In another patient receiving such treatment the blood coagulation time, measured as "prothrombin time," began to drop after the patient had begun daily self-administration of large amounts of ascorbic acid. Two days after the supplemental intake of the vitamin had been discontinued the prothrombin time returned to the elevated level that was desired for treatment of the embolism (129).

Hemolysis of erythrocytes

Large amounts of ascorbic acid given intraperitoneally to mice resulted in some hemolysis of the erythrocytes (130). In experiments with human adults, 5 g ascorbic acid were given daily in 3 divided doses (131).
The percentage of lysis rose from a base of about 3 percent to about 9 percent. The authors suggested that such lysis could account for the hemolysis of erythrocytes in persons who have depressed mechanisms for handling oxidant stress, such as occurs in glucose-6-phosphate dehydrogenase deficiency.

**Effect on human electroencephalogram**

Some evidence indicates that ascorbic acid may have significant effects upon central adrenergic neural processes. Using the electroencephalogram (EEG) to record changes in the central adrenergic states, Kerxhalli et al. (132) in 1975 administered 4 g ascorbic acid orally to each of 18 healthy adolescent boys 27 and 3 hours prior to recording the EEG responses to each of several photic stimulation trials. Following at least 4-day intervals to allow the administered ascorbic acid to be "cleared from the system", the trials were repeated using 50 mg doses of ascorbic acid or a placebo. The 4 g doses produced a significant increase in EEG photic driving responses as compared with 50 mg and placebo doses. Whether the responses signify any harmful effects is not known. Possibly they were related to catecholamine metabolism (133).

**Immunity and microbicidal processes**

Shilotri and Bhat (134) studied the effects of ingesting daily 2 g doses of ascorbic acid on the bactericidal and hexose monophosphate-pentose pathway (HMPP) activities of the leukocytes obtained from 5 normal young men. After 2 weeks the HMPP activity of resting leukocytes increased and the bactericidal activity was impaired. Smith et al. (135) reported that physiological concentrations of ascorbic acid inhibit the phagocytosis of Candida albicans by human granulocytes in vitro, but they were "unaware of an increased incidence of fungal infections in subjects ingesting massive quantities of L-ascorbic acid."

**Teratogenicity**

Reported studies of the possible toxicity and teratogenicity of ascorbates have yielded inconsistent results. Reid (136) found that ascorbic acid was toxic to chick embryos when injected into the air cells at 96 hours at levels of 40 mg per kg and above, but it was not teratogenic at levels up to 200 mg per kg.

Ascorbic acid given by oral intubation at doses up to 520 mg per kg body weight to pregnant mice and up to 550 mg per kg to pregnant rats for 10 consecutive days starting on day 6, had no clearly discernible effect on maternal or fetal survival (137). The number of soft tissue and skeletal abnormalities in the test group did not differ from the number occurring spontaneously in sham-treated controls.
The same negative teratologic results were observed in similar tests with sodium erythorbate in which pregnant mice received up to 1030 mg per kg body weight and pregnant rats up to 900 mg per kg (138).

Naber (139) reported that sodium ascorbate produces a chick embryotoxic response that was closely related to the dose administered. This was evidenced by a high level of embryonic mortality at larger doses and an increase in the percent of abnormal chicks hatched when mortality was between 10 and 80 percent. The histopathological findings, although suggesting some treatment effect, were not statistically significant due to their low incidence. The LC50 at 96 hours via the air cell was about 100 mg per kg. The same investigator found sodium erythorbate to have an embryotoxic effect that was closely related to the dose administered (140). There was a high level of embryonic mortality and an increase in the percentage of abnormal chicks hatched, particularly when given at 96 hours via air cell injection. Histopathological findings were not significant due to low incidence. The LC50 at 96 hours via the air cell was about 84 mg per kg.

Calcium ascorbate solution administered via the air cell and the yolk at 0 and 96 hours of incubation at dose levels ranging from 10 to 200 mg per kg (air cell and yolk at 0 hours), and 5 to 100 mg per kg (air cell and yolk at 96 hours) was moderately lethal to the chicken embryo, but displayed no teratogenicity under the test conditions employed (141). Hwang (142) stated that "Erythorbic acid was found to be quite embryotoxic when administered to the embryos under all conditions of the test." The tests included administration of a water solution via the air cell and via the yolk both at preincubation and at 96 hours of incubation. However, it was concluded on the basis of the different tests in chick embryos that "the teratogenicity of erythorbic acid cannot be ascertained."

**Mutagenicity**

Neither ascorbic acid nor erythorbic acid was mutagenic in a series of in vitro assays using *Salmonella typhimurium* and *Saccharomyces cerevisiae* with and without metabolic activation (143, 144).

In mice, sodium erythorbate was not mutagenic in the host-mediated assay using *S. typhimurium* nor did it increase the mitotic recombination frequency in the host-mediated *S. cerevisiae* D3 assay (145). Sodium erythorbate was not mutagenic to five strains of *S. typhimurium* in vitro either in the presence or absence of metabolic activation. At a concentration of 5 percent, sodium erythorbate did not increase the mitotic recombination frequency of *S. cerevisiae* D3.
Dominant lethal tests produced no consistent responses to suggest that sodium erythorbate is mutagenic in the rat (145). An extensive translocation study in which sodium erythorbate was added to the diet over a 7-week period did not induce translocation heterozygosity in male mice (145). Plate tests and nonactivation and activation suspension tests using *S. typhimurium* and *S. cerevisiae* revealed no mutagenic activity for sodium ascorbate and calcium ascorbate (146,147).
L-ascorbic acid, vitamin C, occurs in nutritionally significant amounts as a natural constituent of many fruits, vegetables, berries, and melons. As a vitamin it is needed in the diet of all age groups. L-ascorbic acid and its sodium salt are antioxidants and they are extensively used as preservatives, color stabilizers and for related functions in various foods and beverages. Calcium ascorbate and ascorbyl palmitate, a derivative of ascorbic acid having greater fat solubility, also are antioxidants, but appear not to have significant use in processed foods.

In addition to their use in foods as antioxidants, L-ascorbic acid and its salts are added to some foods as a source of vitamin C. These sources constitute a significant proportion of the total ascorbate intake of the general population.

Erythorbic acid (D-isoascorbic acid), a stereoisomer of L-ascorbic acid, and its sodium salt, also are effective antioxidants and are used for this purpose in a number of food products. The quantities used in 1970 were substantially less than for the ascorbates. The vitamin activity of erythorbates is only one-twentieth that of ascorbic acid, and their antioxidant effectiveness is not greater than for the ascorbates. For this reason, it would seem desirable, where possible, to use L-ascorbic acid rather than erythorbic acid as an antioxidant.

From studies in guinea pigs and man it can be concluded that although erythorbic acid shares the same absorption and tissue uptake system as ascorbic acid it has little antiscorbutic activity. Although competition between ascorbic acid and erythorbic acid has been demonstrated at a biochemical level, there is no firm evidence that such competition will produce a scorbutic state. Whether this biochemical interaction could result in a clinically significant depletion of ascorbic acid remains to be established.

Both short- and long-term toxicity studies have demonstrated tolerance without adverse effects for large amounts of orally administered L-ascorbic acid, sodium L-ascorbate, and erythorbic acid in several species including mice, rats, guinea pigs, rabbits, and dogs.

A substantial number of short-term experiments with human subjects ingesting 1 to 4 g of ascorbate daily have generally not revealed any harmful effects. Some subjects have received higher amounts, up to at least 8 to 10 g per day. In most instances no untoward results have been noted. But there is marked paucity of such studies that were well controlled and in which inquiring attention was given to possible harmful effects. In due course, such studies would be desirable.
In the various studies on the effects of ingesting excessive amounts of ascorbates, attention has been focused on questions including oxalate excretion and renal tract stones, effects on the utilization of copper, iron, and other metals, need for vitamin B₁₂, blood coagulation, and reproductive performance. The findings indicate that the tolerance to excessive amounts of ascorbic acid and its sodium salt is high. Several investigators have reported the development of dependency in animals and humans after ingestion of large amounts of ascorbates for extended time periods; however, the levels of ascorbate intake in these studies exceeded the estimated daily intakes of ascorbates added to foods by 1 to 3 orders of magnitude.

It is notable that no data have been found concerning the possible effects of ascorbyl palmitate and calcium ascorbate in humans, and there is practically no information regarding the latter in animals. Information concerning ascorbyl palmitate in animals is almost as limited. The few meaningful experiments suggest that ascorbyl palmitate is tolerated about the same as ascorbic acid and sodium ascorbate. This should be expected. It is reasonable to assume that the tolerance to calcium ascorbate is approximately the same as for sodium ascorbate and this is at a high level.

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

There is no evidence in the available information on L-ascorbic acid, sodium L-ascorbate, calcium L-ascorbate, ascorbyl palmitate (palmitoyl L-ascorbate), erythorbic acid (D-isoascorbic acid), and sodium erythorbate (sodium D-iso-ascorbate) that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used as food ingredients at levels that are now current or that might reasonably be expected in the future.
VI. REFERENCES CITED


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139. Naber, E. C. Undated. Investigations on the toxic and teratogenic effects of GRAS substances on the developing chick embryo: [sodium ascorbate]. Prepared under DHEW contract no. FDA 72-343. The Ohio State University, Columbus, Ohio. [15 pp.]

140. Naber, E. C. Undated. Investigations on the toxic and teratogenic effects of GRAS substances on the developing chick embryo: [sodium erythorbate]. Prepared under DHEW contract no. FDA 72-343. The Ohio State University, Columbus, Ohio. [10 pp.]


142. Hwang, U. K. 1974. Investigations of the toxic and teratogenic effects of GRAS substances to the developing chicken embryo: erythorbic acid. A report to M. J. Verrett, Food and Drug Administration, Washington, D.C. St. Louis University School of Medicine, St. Louis, Mo. [9 pp.]


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