EVALUATION OF THE HEALTH ASPECTS OF THE TOCOPHEROLS
AND α-TOCOPHERYL ACETATE AS FOOD INGREDIENTS

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

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

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

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

C. Jelleff Carr, Ph.D., Director
Life Sciences Research Office
FASEB
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I. INTRODUCTION

This report concerns the health aspects of using tocopherols and \( \alpha \)-tocopheryl acetate as food ingredients. It has been based partly on the information contained in a scientific literature review (monograph) furnished by FDA (1), which summarizes the world's scientific literature from 1920 through 1973.* In addition, the Select Committee was provided with an annotated bibliography on tocopherols prepared by the Scientific Literature Department, Hoffmann-LaRoche, Inc. (2). To assure completeness and currency as of the date of 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 February 13, 1976 (41 FR 6787 and 6788) 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 tocopherols and \( \alpha \)-tocopheryl acetate as food ingredients. The Select Committee received no requests for such a hearing on tocopherols and \( \alpha \)-tocopheryl acetate.

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321(s)], GRAS substances are exempt from the premarketing clearance that is required for food additives. It is stated in the Code of Federal Regulations 21 CFR 121.1, revised April 1, 1975 that GRAS means general recognition of safety by experts qualified by scientific training and experience to evaluate the safety of substances on the basis of scientific data derived from published literature. This section of the Code also indicates that expert judgment is to be based on the evaluation of results of credible toxicological testing or, for those substances used in food prior to January 1, 1958, on a reasoned judgment founded in experience with common food use, and is to take into account reasonably anticipated patterns of consumption, cumulative effects in the diet, and safety factors appropriate for the utilization of animal experimentation data. FDA recognizes further (21 CFR 121.3) that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

*The document (PB-221 237/l)is available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.
The Select Committee on GRAS Substances of LSRO is making its evaluations of these substances in full recognition of the foregoing provisions. In reaching its conclusions on safety the Select Committee, in accordance with FDA's guidelines, is relying primarily on the absence of substantive evidence of, or reasonable grounds to suspect, a significant risk to the public health. While the Select Committee realizes that a conclusion based on such reasoned judgment is expected even in instances where the available information is qualitatively or quantitatively limited, it recognizes that there can be instances where, in the judgment of the Select Committee, there are insufficient data upon which to base a conclusion. The Select Committee, aware that biological testing is dynamic, bases its conclusions on information now available; it cannot anticipate the results of experiments not yet conducted or those of tests that may be reconducted, using new technologies. These conclusions will need to be reviewed as new or better information becomes available.

In this context, the LSRO Select Committee on GRAS Substances has reviewed the available information on tocopherols and α-tocopheryl acetate 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

The tocopherols are a group of chemically related substances that possess vitamin E activity. Eight d-form tocopherols occur naturally in many plant and animal tissues; however, d-α-tocopherol is the most widely distributed. In addition, this form is the most effective antioxidant of the naturally occurring forms (3-5). The tocopherols are present in vegetable oils, cereals, nuts, and leafy vegetables. Vegetable oils are the most important sources; wheat germ and cottonseed oils contain d-α-tocopherol as the major tocopherol (4).

In addition to naturally occurring and synthetic d-α-tocopherol, six other tocopherol derivatives are prepared commercially for use as antioxidants in food. Mixed tocopherols concentrate, d-α-tocopheryl acetate concentrate, d-α-tocopheryl acetate and d-α-tocopheryl acid succinate are produced from edible vegetable oils and their by-products; in addition, dl-α-tocopherol and its acetate ester are made synthetically (1, 3, 4). The specifications for tocopherols listed in the Food Chemicals Codex (6) are summarized in Table I.

The Code of Federal Regulations (7) lists tocopherols as GRAS as chemical preservatives and as nutrients and/or dietary supplements. Tocopherol (tocopheryl) acetate also is GRAS as a nutrient and/or dietary supplement. The Select Committee is aware that naturally occurring forms other than d-α-tocopherol are rarely, if ever, used in foods as antioxidants. However, the Select Committee presumes that the generic GRAS term,
<table>
<thead>
<tr>
<th>Product</th>
<th>Composition</th>
<th>Arsenic</th>
<th>Heavy metals (as lead)</th>
<th>Lead</th>
<th>Free fatty acids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>dl-α-Tocopherol</strong></td>
<td>≤97.0% C\textsubscript{39}H\textsubscript{50}O\textsubscript{2}</td>
<td>≤3.0</td>
<td>≤40.0</td>
<td>≤10.0</td>
<td></td>
</tr>
<tr>
<td>Tocopherols concentrate,</td>
<td>≥34.0% total tocopherols, of which</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥50.0% d-α-tocopherol</td>
<td>≤3.0</td>
<td>≤40.0</td>
<td>≤10.0</td>
<td>limit about 2.8% as oleic acid</td>
</tr>
<tr>
<td>d-α-Tocopheryl acetate</td>
<td>≤97.0% C\textsubscript{31}H\textsubscript{52}O\textsubscript{8}</td>
<td>≤3.0</td>
<td>≤40.0</td>
<td>≤10.0</td>
<td></td>
</tr>
<tr>
<td>dl-α-Tocopheryl acetate</td>
<td>≤97.0% C\textsubscript{31}H\textsubscript{52}O\textsubscript{3}</td>
<td>≤3.0</td>
<td>≤40.0</td>
<td>≤10.0</td>
<td></td>
</tr>
<tr>
<td>d-α-Tocopheryl acetate</td>
<td>≥25.0% d-α-tocopheryl acetate;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>concentrate</td>
<td>≥64.0% d-α-tocopheryl acetate of total</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>tocopherols present</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d-α-Tocopheryl acid succinate</td>
<td>≤97.0% C\textsubscript{33}H\textsubscript{54}O\textsubscript{5}</td>
<td>≤3.0</td>
<td>≤40.0</td>
<td>≤10.0</td>
<td></td>
</tr>
</tbody>
</table>
"tocopherols" could mean all naturally occurring as well as commercially prepared forms and has included these in this report.

Although used in foods as antioxidants, the tocopherols are recognized as a group of lipid-soluble compounds with vitamin E activity. Many animal species require vitamin E for normal reproduction, muscle integrity, erythrocyte stability, and several other biochemical and physiological processes (4, 8, 9). An international unit of vitamin E is equal to 1.0 mg of synthetic dl-α-tocopheryl acetate, 0.74 mg of the natural form of d-α-tocopheryl acetate or 0.67 mg of d-α-tocopherol (4, 8). The Food and Nutrition Board, NAS/NRC (9) has established Recommended Daily Dietary Allowances ranging from 4 to 15 I. U. for low-birth-weight and other infants, children and adults. The status of human requirements has been reviewed by Horwitt (10) in a recent international symposium on vitamin E.

Mixed tocopherols concentrate, d-α-tocopherol and its acetate ester were first used as antioxidants in food in 1949; d-α-tocopheryl acetate was first used in 1960, and the d-α-tocopheryl acetate concentrate was first used in 1965 (1, 3). As indicated in Table II, the use of d-α-tocopheryl acetate increased approximately ninefold and that of dl-α-tocopheryl acetate increased approximately 102-fold between 1960 and 1970. The Select Committee has no information concerning the extent to which the increases reflect addition of greater amounts of the two tocopheryl acetates or addition of the two substances to a greater variety of foods.

III. CONSUMER EXPOSURE DATA

A subcommittee of the National Research Council (NRC) surveyed manufacturers by questionnaire concerning the addition of GRAS substances to foods (II). Based on information supplied by those manufacturers who reported adding the substances to at least one food product in a category, weighted means were calculated for the usual and maximal percentage addition of the substance to foods in the categories. Weighted mean percentage of the usual levels of addition calculated by this approach are presented in Table III.

The NRC subcommittee estimated possible average daily intakes (Table IV) from data on the mean frequency of eating foods by food category (Market Research Corporation of America, Chicago, Illinois 60606), U.S. Department of Agriculture data on mean portion size of foods in these categories and the assumption that all food products within a category contain the substance at the level shown in Table III. Such an assumption is likely to lead to overestimates of intake. The NRC subcommittee has recognized that in most cases its calculations of possible intakes are overstated, often by
<table>
<thead>
<tr>
<th>Substance</th>
<th>Relative amounts used*</th>
<th>Total used in 1970†</th>
<th>Per capita daily intake mg*</th>
</tr>
</thead>
<tbody>
<tr>
<td>d-α-Tocopheryl acetate</td>
<td>9</td>
<td>8300</td>
<td>0.11</td>
</tr>
<tr>
<td>d-α-Tocopheryl acid succinate</td>
<td>1</td>
<td>25</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>dL-α-Tocopherol</td>
<td>102</td>
<td>36000</td>
<td>0.48</td>
</tr>
<tr>
<td>Tocopherol concentrate, mixed</td>
<td>0.5</td>
<td>280</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Based only on the reports from those respondents to the NRC survey who submitted information for both 1960 and 1970 (II). Total usage is based on the sum of kilograms used in foods as supplied by NRC (National Research Council) and FEMA (Flavoring Extract Manufacturers' Association) recalculated to 100 percent from survey data that the NRC subcommittee estimated to represent about 60 percent of the actual usage.

†Based on total consumption 1970 and a U.S. population of 205 million.
<table>
<thead>
<tr>
<th>Food category</th>
<th>d-α-tocopheryl acetate</th>
<th>d-α-tocopheryl acid succinate</th>
<th>dl-α-tocopheryl acetate</th>
<th>dl-α-tocopherol concentrate, mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weighted mean percent</td>
<td>Weighted mean percent</td>
<td>Weighted mean percent</td>
<td>Weighted mean percent</td>
</tr>
<tr>
<td>Baked goods, baking mixes</td>
<td>0.040</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breakfast cereals</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milk, milk products</td>
<td>0.001</td>
<td>0.001</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Poultry products</td>
<td>0.005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gelatins, puddings, fillings</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soups, soup mixes</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snack foods</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beverages, nonalcoholic</td>
<td></td>
<td></td>
<td>0.013</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dairy products analogs</td>
<td></td>
<td></td>
<td>0.050</td>
<td></td>
</tr>
<tr>
<td>Seasonings and flavors</td>
<td></td>
<td></td>
<td></td>
<td>0.050</td>
</tr>
<tr>
<td>Baby formulas</td>
<td>0.001</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
</tbody>
</table>

Blanks in the table mean that the substance is not added to foods in the categories indicated. Level of addition of tocopherols is the weighted mean of the levels reported by manufacturers as their usual addition to one or more products in a food category. No reports of addition of dl-α-tocopherol were received by the NRC subcommittee. For discussion of weighted mean see Section X and Exhibit 50 of reference 11.
<table>
<thead>
<tr>
<th>Substance</th>
<th>0-5 Months</th>
<th></th>
<th>6-11 Months</th>
<th></th>
<th>12-23 Months</th>
<th></th>
<th>2-65+ Years</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg</td>
<td>mg/kg</td>
<td>mg</td>
<td>mg/kg</td>
<td>mg</td>
<td>mg/kg</td>
<td>mg</td>
<td>mg/kg</td>
</tr>
<tr>
<td>d-α-Tocopheryl acetate</td>
<td>5.0</td>
<td>1.0</td>
<td>2.4</td>
<td>0.3</td>
<td>1.9</td>
<td>0.2</td>
<td>1.8</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>d-α-Tocopheryl acid succinate</td>
<td>1.4</td>
<td>0.3</td>
<td>10.2</td>
<td>1.3</td>
<td>21.8</td>
<td>2.0</td>
<td>54.9</td>
<td>0.9</td>
</tr>
<tr>
<td>dl-α-Tocopheryl acetate</td>
<td>0.1</td>
<td>&lt;0.1</td>
<td>3.6</td>
<td>0.5</td>
<td>4.0</td>
<td>0.4</td>
<td>3.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>dl-α-Tocopherol</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Tocopherols concentrate, mixed</td>
<td>4.1</td>
<td>0.8</td>
<td>0.8</td>
<td>0.1</td>
<td>0.3</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>

Calculation of mg per kg of body weight was based on an average weight of 60 kg for an adult (12) and the following estimated weights of infants by age group: 0-5 mo, 5 kg; 6-11 mo, 8 kg; and 12-23 mo, 11 kg (13).
considerable margins. * Because of factors detailed in Section XI, the subcommittee stated that the average estimated total dietary intakes are likely to be much higher than would be the intakes achieved through consumption of a diet consisting totally of processed foods to which the substances had been added at the maximum levels (II).

The Select Committee believes the average intakes calculated by the NRC subcommittee (Table IV) could be achieved only by a small fraction of the population. For example, the "average" intake of \( \alpha \)-tocopherol acid succinate for individuals over 2 years of age is estimated to be 54.9 mg per day (Table IV), whereas the total annual consumption in 1970 divided by a U.S. population of 205 million gives an intake of less than 0.01 mg per day (Table II). The "average" intake of this tocopherol appears to be high, probably because the concentration used in baked goods - baking mixes given in Table III is in error. The concentration of 0.04 percent almost certainly applies to some of the dry baking mixes and not to all baked goods as consumed. This error in concentration affects all age groups in Table IV.

A discrepancy between values in Tables II and IV should also be noted for \( \alpha \)-tocopherol acetate. The Select Committee believes that Table II offers reasonable estimates of average consumption of added tocopherols by individuals over 2 years of age and suggests that the estimates in Table IV are erroneously high.

According to label declarations, commercially prepared infant formulas generally provide approximately 5 I. U. of vitamin E per liter; an unspecified portion of this vitamin E is added, presumably in the form of \( \alpha \)-tocopherol acetate or tocopheryl acetate or tocopherols concentrate mix. The NRC subcommittee estimates (Table III) of "usual" additions of tocopherols to infant formulas are unexplainably high. Presumably this high value accounts for the high intake estimates in Table IV for infants less than 6 months of age. The Select Committee finds no logical basis for the estimated greater daily intakes of several tocopherols by infants 6 to 23 months of age than by adults.

With the exception of infants receiving commercially prepared formulas, the quantity of tocopherols added to foods appears to account for a relatively small percentage of total tocopherol intake. Based on total

*An explanation for such overstatements is detailed in Section XI, "Significance and Use of Data in Safety Evaluations," of the NRC subcommittee's report (II). The Select Committee finds this explanation reasonable, and concurs in the first recommendation in Section XII of the same report, that "In order to conduct a more accurate survey on the intake of substances used in food processing, food consumption data collected specifically for this purpose are needed."

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quantity used in foods, the mean per capita daily intake of tocopherols added to foods is approximately 0.6 mg (Table II). Other information suggests that the vitamin E content as tocopherols of the average diet is about 7 to 9 mg but varies widely depending upon the amount and types of animal and vegetable fat as well as the proportions in which these are consumed (9). Bunnell et al. (14) reported an average daily consumption of 7.4 mg (range 2.6 to 15.4 mg) and Bieri and Evarts (15) have recently reported an average daily consumption of 9.0 mg (range 4.4 to 12.7 mg). Both estimates are based on analyses of foods as consumed.

In its evaluation of α-tocopherol and mixed tocopherols concentrate, the Joint FAO/WHO Expert Committee on Food Additives (16) concluded that, based on clinical experience, an acceptable daily intake for men would be not more than 2.0 mg per kg body weight α-tocopherol or its equivalent. For the average adult male of 60 kg (12), this would be 120 mg per person per day, a figure at least 15 times the possible average daily total intake estimated by Bunnell et al. (14) and Bieri and Evarts (15).

IV. BIOLOGICAL STUDIES

Absorption and metabolism

Not all ingested tocopherols in raw foods are available for absorption. Numerous studies have shown that the vitamin E activity of tocopherols in foods may be destroyed by cooking (1). Commercial processing and storage result in relatively larger losses of tocopherols than those resulting from ordinary cooking (14). Thus, both naturally occurring and added tocopherols in ingested foods may not necessarily be absorbed by the intestine.

According to Horwitt (4), there is no significant difference in the rate at which the several tocopherols are absorbed from the intestine. The tocopheryl acetate derivatives are partially hydrolysed by intestinal esterases and absorbed; they are also partially absorbed as intact esters. Pearson and Barnes (17) observed that α- and δ-tocopherols are absorbed more rapidly than the β- or γ-forms. They injected 600 to 800 μg of each tocopherol in 0.2 ml glycerol trioleate into isolated intestinal loops of female hooded rats. After 6 hours, absorption of the α-, β-, γ-, and δ-tocopherols was 32, 18, 1.8 and 30 percent, respectively.

The importance of bile in the absorption of tocopherols from the intestinal tract has not been clearly established. Although it was reported that bile promotes absorption of dl-α-tocopheryl acetate in the rat (18), Greaves and Schmidt (19) and Sternberg and Pascoe-Dawson (20) presented
data that did not support this view. Weber et al. (21, 22) observed that the oral administration of \( \alpha \)-tocopherol and \( \alpha \)-tocopherol in a 1:1 ratio resulted in a 55 percent greater absorption of each than when fed singly. In addition, they found that \( \alpha \)-tocopherol is absorbed and excreted more rapidly than \( \alpha \)-tocopherol. In the rat, \( \alpha \)-tocopherol absorption is mainly via lymphatic pathways and by the portal vein (23). Based on studies with dogs fed several tocopherols, Kaludin (24) suggested that \( \beta \), \( \gamma \), and \( \delta \)-tocopherols are converted to \( \alpha \)-tocopherol in the body. However, Dju et al. (25) found no evidence for conversion of either \( \gamma \)- or \( \delta \)-tocopherols to \( \alpha \)-tocopherol in laying hens fed either isomer.

In man, physiologically active amounts of tocopherols are readily absorbed in the gastrointestinal tract and distributed throughout the body tissues. Depending upon the amount ingested, a significant amount may be excreted unchanged in the feces. For example, Schmandke et al. (26) reported the following data on absorption of \( \alpha \)-tocopherol in thirty 18 to 34 year old men:

<table>
<thead>
<tr>
<th>Oral Dose (mg)</th>
<th>Percent Absorbed (24 hrs.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>96.9 ± 13.0</td>
</tr>
<tr>
<td>30</td>
<td>87.3 ± 13.5</td>
</tr>
<tr>
<td>50</td>
<td>72.6 ± 11.6</td>
</tr>
<tr>
<td>100</td>
<td>81.5 ± 6.1</td>
</tr>
<tr>
<td>500</td>
<td>67.6 ± 19.4</td>
</tr>
<tr>
<td>1500</td>
<td>70.3 ± 27.9</td>
</tr>
<tr>
<td>2000</td>
<td>55.2 ± 28.8</td>
</tr>
</tbody>
</table>

Following the oral administration of 0.5, 1.0, 1.5, and 2.0 g of \( \alpha \)-tocopherol to healthy male test subjects, Schmandke (27) recovered from the urine 3.11, 12.32, 8.18 and 9.31 mg, respectively, of the compound in the form of tocopheronolactone. Simon et al. (28) have reported that the oral administration of 3 to 5 g of \( \alpha \)-tocopherol to human subjects resulted in two metabolites, mainly conjugated 2(3-OH-4-CH\(_3\)-5-carboxy-pentyl)-3,5,6-trimethyl-benzoquinone and its gamma lactone.

After oral administration of 1 g \( \alpha \)-tocopherol to healthy men, Schmandke and Schmidt (29) found that about 40 percent is absorbed and that 6 percent of the absorbed tocopherol is reduced to tocopheronolactone; of 1 g of orally administered \( \alpha \)-tocopherinone, about 75 percent is absorbed and 1.8 percent of that absorbed is reduced to tocopheronolactone. On the basis of the low rate of change of \( \alpha \)-tocopherinone to tocopheronolactone in comparison with \( \alpha \)-tocopherol, the authors suggested that the mechanism of \( \alpha \)-tocopherol catabolism is by way of \( \alpha \)-tocopherinone to tocopheronolactone in man.
In subjects receiving oral doses of 2.0 g \( \alpha \)-tocopherol or \( \alpha \)-tocopheryl acetate, Gounelle et al. (30) found that \( \alpha \)-tocopherol is more readily absorbed than the acetate form and that peak blood levels for both forms occurred at 6 hours after ingestion and absorption.

In man, bile appears to be involved in the absorption of tocopherols; normally, at least 50 percent of the oral dose is absorbed, and the remainder is excreted unchanged in the feces. In addition, limited breakdown results in production of urinary metabolites. MacMahon and Neal (31) administered oral doses of tritium-labeled \( \alpha \)-tocopherol to seven fasted normal subjects and found that 55 to 79 percent of the dose was absorbed and 3 to 16 percent of the total radioactivity was recovered from the urine in 3 days. Peak plasma levels were reached in 5 to 9 hours; and they calculated that the metabolic half-life was 53 hours. Radioactivity in the blood plasma was almost all associated with free \( \alpha \)-tocopherol. These investigators also observed relatively poorer absorption of tocopherol in patients with malabsorption problems, biliary obstruction, steatorrhea, and gastrectomies than that in normal subjects. In another study, Kelleher et al. (32) found essentially similar patterns of absorption in 50 fasting subjects given tritium-labeled dl-\( \alpha \)-tocopherol orally. Six to 12 hours after administration, absorption was 72 percent; after 6 to 12 days, less than 6 percent of the activity was recovered in the urine and 80 percent was found in the plasma as unchanged \( \alpha \)-tocopherol. Subjects with steatorrhea absorbed less (59%) than those without steatorrhea (72%).

Blomstrand and Foresgren (33) fed two patients with cannulated thoracic ducts a formula meal with doses of several tritium-labeled derivatives of tocopherol and then analyzed lymphatic lipids serially for up to 24 hours. Absorption of the tocopherols was 21 to 91 percent of the administered dose within 24 hours. Peak absorption occurred 2 to 8 hours after dosing; the major portion of the recovered radioactivity was located in the chylomicrons. These investigators concluded that tocopherol and tocopheramine are absorbed via the lymphatic pathway in man, and enter the thoracic duct intact; but that the acetate derivative is split after absorption and is recovered as tocopherol. They concluded that ingestion of a diet high in polyunsaturated fatty acids increases the requirement for vitamin E and could result in a deficiency state.

In some premature infants, fat-soluble forms of \( \alpha \)-tocopheryl acetate are poorly absorbed (34, 35). Hemolytic anemia has been described in premature infants receiving commercially prepared formulas containing iron and high concentrations of polyunsaturated fatty acids (35-37). The anemia responds to treatment with water-soluble forms of tocopherols.

The distribution of \( \alpha \)-tocopherol in the rat was determined with both carbon-14 labeled and unlabeled dl-\( \alpha \)-tocopherol administered orally. A rapid uptake by the liver was noted (maximum after 4 hours); however, redistribution in the body occurred rapidly. The highest concentration of radioactivity was found in the adrenal glands and high radioactivity was present
in the pituitary, heart, liver, kidney, fat, testes and skin. Radioactivity was present 88 days after dosing with the highest activity in the brain (39). The percentage intracellular distribution of radioactivity 24 hours after the oral administration of α-[5-methyl-14C] tocopherol in the spleen has been reported to be: mitochondria, 59 percent; microsomes, 19 percent; supernatant, 12 percent. In the liver, distribution was as follows: mitochondria, 12 percent; microsomes, 44 percent; supernatant, 31 percent; and nuclei, 14 percent (39). Krishnamurthy and Bieri (40) administered carbon-14-labeled α-tocopherol orally to rats (and chickens) and reported that α-tocopherol in rat liver and intestinal mucosal cells was distributed 50 to 60 percent in mitochondrial and 15 to 20 percent in the microsomal and supernatant fractions. They observed that in the plasma, tocopherols appeared in neutral fat and were bound to globulins. Presumably, the distribution of tocopherols in body tissues of other mammals would be similar to that found in the rat.

The metabolic roles and activities of tocopherols have been studied extensively (1, 2, 4). It is recognized that vitamin E is associated closely with lipids throughout the body, stabilizing highly unsaturated fatty acids within the cell and cell membrane against oxidation. Noguchi et al. (41) have suggested that the tocopherols appear to prevent exudative diathesis by neutralizing free radicals within lipid membranes thereby preventing a chain-reactive autooxidation of capillary membrane lipids. Chow et al. (42) concluded that dietary tocopherols may protect erythrocytes against oxidative stress (lipid peroxidation) by regulating the level of reduced glutathione via an effect on the enzyme, glutathione peroxidase.

When administered in relatively small doses the following metabolic effects have been reported:

- Ingestion of 0.12 ml of a 10 mg per g solution of tocopherol (type unspecified) by young chicks resulted in increased agglutinin and complement titers as well as enhanced phagocytic activity of the leucocytes (43); and,

- Injection of 10 mg per day of α-tocopherol for seven days into female golden hamsters (route unspecified) after ovariectomy produced estro-progesterone effects (44).

- A dose of 0.15 mg per rat per day for 10 days depressed the "anticoagulative system activity" (45).

With relatively larger amounts, the following observations have been reported from several animal studies:
• Inclusion of 100 mg per day of \( \alpha \)-tocopheryl acetate in the diet of male albino rats resulted in increased concentrations of adenosine di- and triphosphate and coenzyme A in the liver. (46);

• Administration (route not specified) of 150 to 600 mg per day \( \alpha \)-tocopherol resulted in decreased urinary excretion of thiamine by rats (47);

• Supplementation of daily rations of vitamin E deficient male albino rats with 25, 50, or 100 mg per day of vitamin E (not otherwise identified) for 22 days produced increased concentrations of copper and calcium in the liver, muscle and bone. At the lowest dose, there was a decrease in concentration of iron in liver and muscle; with the intermediate dose, the decrease in concentration of iron in the liver was accompanied by an increase in muscle and bone content. With the largest dose there was an increase in concentration of iron in the liver and muscle but a decrease in bone (48);

• Feeding male albino rats a ration with 100 mg \( \alpha \)-tocopheryl acetate per rat per day for 8 days increased the phospholipids as well as total and esterified cholesterol found in liver homogenates of the experimental but not the control animals (49);

• Dietary supplementation with 150 mg per rat per week of vitamin E concentrate (34 percent mixed tocopherols) administered orally by syringe in ethyl laurate solution for 20 to 27 weeks, resulted in localized sclerosis and deposition of cholesterol in the aorta which were prevented by high dietary cholesterol and bile salt (50).

The number of controlled investigations of the metabolic effects of large doses of tocopherol to human subjects is limited. Baroni and Casa (51) reported that a single intramuscular injection of 300 mg \( \alpha \)-tocopherol in 10 subjects decreased the basal metabolic rate; prolonged administration of 300 mg \( \alpha \)-tocopherol by intramuscular injection on alternate days for 4 weeks to seven patients with elevated basal metabolic rates produced decreases in basal metabolic rates. Oral administration of 100 mg \( \alpha \)-tocopherol acetate to 12 subjects each day for 10 days resulted in greater plasma levels of phospholipids, total cholesterol, and \( \alpha_2 \)-globulins, but a decrease in plasma amino acid levels (52). Prosperi (53) and Furgulio and Petrin (54) have reported shorter blood coagulation times following single oral doses of 100 mg \( \alpha \)-tocopherol.
Toxicity studies

The scientific literature on the effects of vitamin E administered orally or ingested in diets at various dosages is extensive (1,2). In general, these reports document alterations in several parameters of growth, development, and metabolism. The majority of the effects are elicited at dosage levels that exceed by severalfold, the normal daily intake levels. The deviations from the expected norm are eliminated by cessation of dosing with vitamin E.

The \( \text{LD}_{50} \) values for acute oral toxicity of the tocopherols are relatively high (Table V). In addition to these data, Demoie (55) determined that frogs, rabbits, cats, dogs, and monkeys can tolerate without apparent toxic signs, oral doses of 200 mg per kg \( \text{dl-}\alpha\)-tocopherol or tocopheryl acetate.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Species</th>
<th>Route</th>
<th>( \text{LD}_{50} ) mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E, injectable</td>
<td>mouse</td>
<td>i.m.</td>
<td>&gt;250</td>
</tr>
<tr>
<td></td>
<td>rat (adult)</td>
<td>i.m.</td>
<td>&gt;250</td>
</tr>
<tr>
<td></td>
<td></td>
<td>i.p.</td>
<td>&gt;2000</td>
</tr>
<tr>
<td></td>
<td>rabbit</td>
<td>i.m.</td>
<td>&gt;50</td>
</tr>
<tr>
<td>( \text{dl-}\alpha)-Tocopherol</td>
<td>mouse</td>
<td>i.p.</td>
<td>&gt;2000</td>
</tr>
<tr>
<td></td>
<td>s.c.</td>
<td></td>
<td>&gt;2000</td>
</tr>
<tr>
<td></td>
<td>oral</td>
<td></td>
<td>&gt;4000</td>
</tr>
<tr>
<td></td>
<td>rat (neonate)</td>
<td>oral</td>
<td>&gt;4000</td>
</tr>
<tr>
<td></td>
<td>rat (adult)</td>
<td>i.p.</td>
<td>1480</td>
</tr>
<tr>
<td></td>
<td></td>
<td>oral</td>
<td>&gt;4000</td>
</tr>
<tr>
<td></td>
<td>rabbit</td>
<td>oral</td>
<td>&gt;2000</td>
</tr>
<tr>
<td>( \text{dl-}\alpha)-Tocopheryl acetate</td>
<td>mouse</td>
<td>i.p.</td>
<td>&gt;2000</td>
</tr>
<tr>
<td></td>
<td>s.c.</td>
<td></td>
<td>&gt;2000</td>
</tr>
<tr>
<td></td>
<td>oral</td>
<td></td>
<td>&gt;4000</td>
</tr>
<tr>
<td></td>
<td>rat (neonate)</td>
<td>oral</td>
<td>&gt;4000</td>
</tr>
<tr>
<td></td>
<td>rat (adult)</td>
<td>i.p.</td>
<td>840</td>
</tr>
<tr>
<td></td>
<td></td>
<td>oral</td>
<td>&gt;4000</td>
</tr>
<tr>
<td></td>
<td>rabbit</td>
<td>oral</td>
<td>&gt;2000</td>
</tr>
</tbody>
</table>
Demole (55) also observed that mice exhibited no adverse effects from oral doses of 50 g per kg of either dl-α-tocopherol or its acetate ester. Male rats tolerated daily doses of 1.0 per kg dl-α-tocopherol or dl-α-tocopheryl acetate for 10 days while female rats tolerated 0.5 g per kg of either form without toxic effects. Male and female rats received a total dose of 4.0 g per kg of either dl-α-tocopherol or its acetate by stomach tube over a period of two months without any adverse health effects. den Tonkelaar et al. (56) observed that male and female Wistar rats exhibited no adverse effects from a 15 percent lard diet containing 20 to 40 mg per kg (0.002% and 0.004% in the diet) α-tocopherol over 13 weeks.

On the other hand, Ichihara (57) has reported that daily intramuscular administration of 10 mg dl-α-tocopherol acetate for 20 days in mice resulted in enlargement of the testicular interstitial cells and marked enlargement of smooth endoplasmic reticulum. Hütter (58) reported that the oral administration of 5.5 to 12.5 mg tocopherol acetate per kg body weight per day for 1 to 3 months resulted in highly active but normal thyroid glands in female rabbits, and abnormal changes in weight and volume as well as enhanced epithelial cell proliferation in the thyroid glands of male rabbits.

Costa et al. (59) gave guinea pigs α-tocopherol at approximately 13 mg per kg per day by mouth for 10 days. All treated animals developed hyperemia of the thyroid and greater iodine uptake but no other adverse effects were reported. In a series of studies with guinea pigs weighing 250 to 300 g, Prosperi and Borselli (60) found that intramuscular injection of vitamin E (presumably dl-α-tocopheryl acetate) in adult guinea pigs produced the following effects:

- 364 mg per kg per day for 10 days: increase in body weight and no demonstrable pathology;
- 727 mg per kg per day for 10 days: lesser increase in body weight but histologically evident degenerative changes in hepatic and myocardial cells;
- 1091 or 1454 mg per kg (single injection): elicited similar evidence of myocardial, hepatic and neural pathology; and,
- 4363 mg per kg (single injection): resulted in roughened fur, hyperemia of spleen, and hyperplasia of interfascicular endothelia and Kupfer cells of the liver.

In another series of experiments, Prosperi and Borselli (60) observed morphological and histological degeneration of cells in tissues
of several endocrine glands of guinea pigs following intramuscular injection of \textit{dl-\alpha}-tocopheryl acetate at 1091 mg per kg for three days followed by 727 mg per kg for two days. Stimulation of mitotic activity in testicular and ovarian cells was also noted.

Excessive intake of tocopherols leads to hypervitaminosis E in several animal species. Conditions described as hypervitaminosis E have been reported in guinea pigs (60), hamsters (61), rats (62), and chicks (63, 64). Some of the effects reported include changes in estrus cycle (length of phases, periodicity in rats), degenerative lesions of liver and myocardium (following intramuscular administration in guinea pigs). In these instances, the doses used to elicit the effects described are in the range of 1 g per kg body weight.

The oral administration of 296 g \textit{dl-\alpha}-tocopheryl acetate to one human subject over a period of 93 days resulted in gastrointestinal distress and muscle weakness which disappeared when the treatment was stopped (65). Greenblatt (66) fed six male subjects 667 mg per kg \textit{dl-\alpha}-tocopheryl acetate daily for one month. No adverse effects were noted but serum cholesterol was lowered. The oral administration of 0.67 to 0.84 mg per kg of \textit{\alpha}-tocopheryl acetate each day for 9 to 10 days to 26 patients resulted in higher blood tocopherol levels and an increase in thyroid uptake of iodine (59).

Adult humans have tolerated oral doses of 1 g per day of vitamin E for months, or larger doses for shorter periods with no undesirable effects (67). Welch (68) treated 67 patients with lupus erythematosus with preparations of pantothenic acid and \textit{dl-\alpha}-tocopheryl acetate for periods up to three years. Patients received doses of the tocopherol as high as 33 mg per kg per day over this period with no adverse effects beyond transient nausea and gastric distress. Similar massive dosages (up to 33 mg per kg per day) of the vitamin E preparation were also administered to 154 patients with diseases other than lupus and no complications were reported.

There is no convincing evidence that high intake of tocopherols leads to hypervitaminosis E in humans; similarly, physiological benefits from the addition of large amounts of vitamin E to the diet have not been demonstrated. Horwitt and Mason (67) have stated, "No state or syndrome of hypervitaminosis E has been described, nor is there evidence that tocopherols per se exert any deleterious effect in animals or man."

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Recently, Alfin-Slater (69) reported that a hypervitaminosis E is only a possibility in those patients who are ingesting very large amounts of vitamin E (over 400 mg per day) for long periods of time. Cohen (70) reported that ingestion of 564 mg of α-tocopherol daily for 7 days resulted in fatigue, malaise, and loss of energy. The clinical symptoms disappeared when the treatment was withdrawn. He suggested that patients with "fatigue" who were consuming large doses of vitamin E might exhibit similar symptoms because of the vitamin intake. In view of the estimated average daily adult intake of all tocopherols added to foods (0.6 mg), the probability of reaching intake levels in excess of 400 mg per day is extremely remote.

No reports of controlled long-term studies on the possible toxicity of tocopherols to man have come to the attention of the Select Committee.

Special studies

Reproduction. Telford et al. (71) administered total doses of 1.0 g per kg dl-α-tocopheryl acetate, in the diet to pregnant Walter Reed-Carsworth Farms rats for 20 days during gestation. Similar experiments were run using 350 mg and 1.0 g per kg dl-γ-tocopherol. Based on fetal resorption data, they concluded that both maternally administered compounds reduced the frequency of resorption below that in the control animals except for 14.0 percent reabsorptions with the dl-α-tocopheryl acetate administered at 500 mg per kg. In studies with other animals, the daily subcutaneous administration of 75 mg dl-α-tocopherol acetate to male adult hamsters for 8 to 30 days resulted in significantly lower testicular weights than those of control animals, a transitional disruption in spermatogenesis, but no alteration in testicular endocrine function (61). The addition of dl-α tocopherol to the feed (20 mg per lb) of Broad Breasted Bronze turkey hens resulted in a slight increase in hatchability (72). The parenteral administration of a total dose of 3,000 mg of dl-α-tocopherol over a 10-week period to male and female chicks resulted in inhibited growth, including delay of sexual maturity in males, but not in females (73).

Using normal adolescent school girls as subjects, Winkler (74) observed that the oral administration of 30 mg of α-tocopherol daily for one or two menstrual cycles, resulted in an increase in urinary hormone excretion. He suggested that these latter effects may involve the anterior pituitary.

Mutagenicity. The Select Committee has not found any specific tests of mutagenic activity of the several tocopherols that are generally recognized as safe. However, tests with plant material suggests that vitamin E may protect meristematic cells from radiation damage (75).
Teratology. The administration of oral doses up to 1600 mg per kg body weight of dl-α-tocopherol acetate immediately after conception to mice and rats for 10 days, to hamsters for 5 days, and to rabbits for 13 days had no discernible effects on nidation or on maternal or fetal survival (76). However in the tests with pregnant rabbits at 0, 16.0, 74.3, 345.0 and 1600.0 mg per kg, one of the 16 animals in the control group died; two of 16 died at the 16 mg per kg level; three of 20 at the 74.3 mg per kg level died; two of 18 receiving 345.0 mg per kg died; and six of 19 died at the highest dosage level (76). Soliman (77) has reported that simultaneous injection of 0.1 g α-tocopherol diminishes the teratogenic effects of vitamin A palmitate (250,000 I.U.) in rats. Reid (78) has reported that dl-α-tocopheryl acetate failed to demonstrate a significant increase in the occurrence of abnormalities in the avian embryo teratology test series at doses from 16.0 to 120.0 mg per kg.

Carcinogenicity. Telford (79) measured the growth of lung tumors in mice at three levels of d-α-tocopherol in the diet. The tumors were induced in susceptible mice (Bar Harbour hereditary lung tumor strain) with 1.0 mg of the carcinogen, 1,2,5,6-dibenzanthrene. At seven months, mice on a stock diet and on a diet to which 2.0 mg of d-α-tocopherol was added every other day, had 91 percent and 100 percent tumors, respectively. Mice on a diet deficient in d-α-tocopherol had 71 percent tumors. Telford (79) indicated that the incidence of lung tumors was greatest in the hypervitaminosis groups and that vitamin E deficiency appeared to decrease incidence in this susceptible mouse strain.

Several investigators (80-90) have fed or injected mice or rats with various doses of α-tocopherol, dl-α-tocopherol, or dl-α-tocopheryl acetate and have reported no tumor formation or increased incidence of tumors. Furthermore, the addition of α-tocopherol to the laboratory chow diet of mice at 0.67 g per kg of diet appreciably inhibited the carcinogenic effect of methylcholanthrene (91). The addition of vitamin E (5 percent w/w) to the diet of mice did not affect their response to 3,4,9,10-dibenzpyrene. There was neither significant decrease in body weight nor in average tumor incidence; there was no significant increase in average time to tumor-induced death (92).

In studies of dermal carcinogenicity, the painting of 10 percent dl-α-tocopherol solution in sesame oil on the depilated skin of adult male mice, three times per week for 8 weeks did not elicit any observable effects whereas no growth of hair, thickening and callosity of the skin, as well as papilloma were reported in positive controls treated with benzpyrene in benzene (80). In a companion study, some of the mice that were exposed to benzpyrene were treated with a daily dose of 10 mg dl-α-tocopherol
per os for one month. There were no differences observed between animals that received \( \alpha \)-tocopherol and those that did not. \( \alpha \)-Tocopherol (60 mg per week for 39 to 41 days, per os) did not affect the rate of growth of sarcomas following subcutaneous administration of 1 percent benzpyrene. However, the intraperitoneal administration of \( \alpha \)-tocopherol or its acetate (7 doses, 400 mg per kg each) retarded growth of transplanted tumors and prolonged survival of rats (93). The addition of tocopherols to croton oil decreased the tumor promoting effects of croton oil with respect to tumor initiation by 7,12 dimethyl benzanthracene (94).

Other studies. Tuberculin-type sensitization has been demonstrated in guinea pigs with \( d \)-\( \alpha \)-tocopherol and \( dl \)-\( \alpha \)-tocopherol (95).

V. OPINION

Tocopherols are a natural constituent of many foods. The average daily dietary intake of tocopherols in the United States is approximately 5 to 20 mg. The quantity of tocopherols added to foods as antioxidants is estimated to be equivalent to an average adult daily intake of 0.6 mg.

The several tocopherols used in foods as antioxidants are readily absorbed and metabolized. They are relatively non-toxic. \( LD_{50} \) values for acute oral toxicity of several animal species are in excess of 2000 mg per kg. Hypervitaminosis E has been reported in humans only at oral dosage levels in excess of 400 mg per day. Investigations on mutagenic, carcinogenic, and teratogenic effects of tocopherols have not revealed any deleterious or pathologic alterations, although some reproductive system effects have been observed in young animals fed or administered dosage levels that exceed by manyfold, the quantities added to food or present in the daily diet.

The Select Committee has weighed the foregoing and concludes that:

There is no evidence in the available information on tocopherols and \( \alpha \)-tocopheryl acetate 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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