EVALUATION OF THE HEALTH ASPECTS OF LECITHIN

AS A FOOD INGREDIENT

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 lecithin as a food ingredient. It has been based partly on the information contained in a scientific literature review (monograph) furnished by FDA (1), which summarizes the world's scientific literature from 1920 through 1974.* In addition, the Select Committee was provided with a review of recent literature on the health aspects of lecithin as a food ingredient prepared by LSRO (2).* To assure completeness and currency as of the date of this report, this information has been supplemented by searches of over 30 scientific and statistical reference sources and compendia that are generally available; use of new, relevant books and reviews and the literature citations contained in them; consideration of current literature citations obtained through computer retrieval systems of the National Library of Medicine; searches for relevant data in the files of FDA; and by the combined knowledge and experience of members of the Select Committee and the LSRO staff. In addition, an announcement was made in the Federal Register of April 6, 1979 (44 FR 20797-20800) 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 lecithin as a food ingredient. The Select Committee received no request for such a hearing on lecithin.

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 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 documents (PB-241 970/3 and PB-275 751/6) are 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 evaluation of this substance 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 lecithin and submits its interpretation and assessment in this report, which is intended for the use of FDA in determining the future status of this substance under the Federal Food, Drug, and Cosmetic Act.
II. BACKGROUND INFORMATION

The term lecithin refers to the phospholipid or phosphatide fraction of substances which occur widely in nature and can be isolated from both plant and animal tissues. The term lecithin is also used as a synonym for phosphatidylcholine, one of the major constituents of commercial lecithin. Phosphatidylethanolamine, another major constituent of commercial lecithin, is sometimes termed cephalin. The structures of phosphatidylcholine, phosphatidylethanolamine, and phosphatidylinositol, the major phosphatide constituents of soy lecithin, are shown in Figure I. The chemical composition of lecithin varies with its source.

Commercial food grade lecithin is a complex mixture of phosphatides and other materials derived from the processing of oil seeds (4), principally soybeans (5,6). Generally, food grade lecithin is isolated by hydration of solvent-extracted soybean oil. Lecithin becomes insoluble, coagulates, and is isolated as a gum following hydration of the extracted oil (7,8). The substance is then dried to a low moisture content, preferably less than 1 percent; it may contain up to 35 percent soybean oil (9).

There are six commercial grades of natural lecithin: unbleached, bleached, or double-bleached, each of fluid or plastic consistency (5). Plastic lecithin may be converted into fluid lecithin by increasing the oil or free fatty acid content (5,9). The terms bleached or double-bleached lecithin are not necessarily indicative of the processing of the lecithin but refer to its color. In addition to the six grades of natural lecithin, there are refined and modified lecithins available commercially. Refined lecithins include oil-free lecithins, alcohol-soluble phosphatide fractions, and alcohol-insoluble phosphatide fractions. Modified lecithin includes hydroxylated lecithin, which is more easily dispersed in water and, in some instances, is superior to the natural grades in fat emulsifying properties (9).

Lecithin is listed in the Code of Federal Regulations (3) under 21 CFR 182.1400 as a multiple purpose GRAS food substance. Lecithin bleached with hydrogen peroxide or benzoyl peroxide is also considered GRAS by the FDA, "assuming the absence of residual unreacted peroxide" (10). Lecithin bleached with benzoyl peroxide will be considered in another report of the Select Committee (11). Hydroxylated lecithin is a regulated food additive under 21 CFR 172.814 and is not considered in this report.

As shown in Table I, phosphatidylcholine, phosphatidylethanolamine, and phosphatidylinositol are the major constituents of oil-free soybean lecithin (4). These three phosphatides are not themselves discrete chemical entities since the fatty acids esterified to the numbers 1 and 2 carbon atoms of the glycerol moieties can vary with respect to chain length and number of
FIGURE I

Structures of the Three Major Phosphoglycerides Present in Lecithin

(1) \( \text{CH}_2\text{-O-C-R} \)

(2) \( \text{R-C-O-C-H} \)

(3) \( \text{CH}_2\text{-O-P-O-CH}_2\text{-CH}_2\text{-N(CH}_3)_3 \)

Phosphatidylcholine

\( \text{O} \)

\( \text{CH}_2\text{-O-C-R} \)

\( \text{R-C-O-C-H} \)

\( \text{OH} \)

\( \text{CH}_2\text{-O-P-O-CH}_2\text{-CH}_2\text{-NH}_2 \)

Phosphatidylethanolamine

\( \text{O} \)

\( \text{CH}_2\text{-O-C-R} \)

\( \text{R-C-O-C-H} \)

\( \text{OH} \)

\( \text{CH}_2\text{-O-P-O-CH}_2\text{-CH}_2\text{-NH}_2 \)

Phosphatidylinositol

R refers to the carbon chains of the fatty acids esterified at carbon atoms 1 and 2 of the glycerol moiety.
TABLE I

Composition of a Commercial Sample of Oil-Free Soybean Lecithin

<table>
<thead>
<tr>
<th>Compound</th>
<th>Percent by weight&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phospholipids:</strong></td>
<td></td>
</tr>
<tr>
<td>phosphatidylcholine</td>
<td>29.0 ± 2.1</td>
</tr>
<tr>
<td>phosphatidylethanolamine</td>
<td>23.5 ± 0.7</td>
</tr>
<tr>
<td>phosphatidylinositol</td>
<td>15.1 ± 0.8</td>
</tr>
<tr>
<td>phosphatidic acid</td>
<td>7.0 ± 0.8</td>
</tr>
<tr>
<td>unestimated phospholipids&lt;sup&gt;c&lt;/sup&gt;</td>
<td>7.9 ± 1.2</td>
</tr>
<tr>
<td><strong>Total phospholipids</strong></td>
<td>82.5</td>
</tr>
<tr>
<td><strong>Glycolipids:</strong></td>
<td></td>
</tr>
<tr>
<td>esterified steryl glucosides</td>
<td>6.2 ± 0.3</td>
</tr>
<tr>
<td>steryl glucosides + cerebrosides</td>
<td>3.7 ± 0.3</td>
</tr>
<tr>
<td>digalactosyl diglyceride</td>
<td>1.7 ± 0.3</td>
</tr>
<tr>
<td>unestimated galactolipids&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3.4 ± 0.7</td>
</tr>
<tr>
<td><strong>Total glycolipids</strong></td>
<td>15.0</td>
</tr>
<tr>
<td><strong>Neutral lipids:</strong></td>
<td></td>
</tr>
<tr>
<td>triglyceride</td>
<td>2.0 ± 0.3</td>
</tr>
<tr>
<td>sterols</td>
<td>0.2 ± 0.07</td>
</tr>
<tr>
<td>free fatty acids</td>
<td>0.1 ± 0.01</td>
</tr>
<tr>
<td>unestimated neutral lipids&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.2 ± 0.15</td>
</tr>
<tr>
<td><strong>Total neutral lipids</strong></td>
<td>2.5</td>
</tr>
</tbody>
</table>

<sup>a</sup> Adapted from reference 4.
<sup>b</sup> Mean ± 1 standard deviation.
<sup>c</sup> Unestimated phospholipids include acylphosphatidylethanolamine, diphosphatidyglycerol, lysophosphatidylethanolamine, lysophosphatidylycerol, and unknowns.
<sup>d</sup> The unestimated glycolipids were not identified.
<sup>e</sup> Unestimated neutral lipid included diglycerides, monoglycerides, sterol esters, pigments, and unknowns.
double bonds. The relative fatty acid compositions of soybean oil, lecithin, and oil-free lecithin are shown in Table II. The number 2 carbon atom of the glycerol moiety of the phosphatides found in lecithin is asymmetric. These phosphatides have the same configuration as the parent compound, L-phosphoglyceroic acid, and are of the L-stereoisomeric series (12).

In addition to the three major phosphatides, soybean lecithin (Table I) contains a number of additional compounds such as phosphatidic acid, steryl glucosides, cerebrosides, and triglycerides (4); the actual composition varies somewhat depending on the manufacturing process and the variety of the soybeans (9). Trace amounts of riboflavin, biotin, tocopherol, and other vitamins are reportedly found in soybean lecithin (13).

As in soy lecithin, the major phosphoglycerides found in safflower lecithin are phosphatidylcholine, phosphatidylethanolamine, and phosphatidylinositol (14). Table III shows the phosphoglyceride contents and the fatty acid composition of the individual phosphoglycerides of crude phosphatide fractions from three varieties of safflower oil. One of the safflower varieties (UC-1) has a very high oleic acid content as compared with other safflower varieties or soy lecithin.

Crude soybean oil contains 2 to 3 percent lecithin, and significant amounts are found in corn and wheat oil (8,15). Lecithin is widely distributed in animal tissue. Egg yolk contains about 10 percent lecithin (16). Human and cow milk contain about 60 and 36 mg of phospholipid per 100 ml, respectively (17). Bile contains about 200 and plasma about 160 mg phosphoglycerides per 100 ml. Phosphoglycerides are found in chylomicrons, associated with plasma proteins (18), and are important constituents of cellular and organelle membranes (19).

Lecithin is used commercially for its emulsifying and antioxidant properties in cosmetics and toiletries, paints, lacquers and printing inks (5). It is also used in leather and textile manufacture (4).

In food processing, lecithin is used as an emulsifier and antioxidant in candy, chocolate, margarine, baked goods, macaroni, milk products, and edible fats and oils (5,20). Large amounts are used in the manufacture of chocolate to lower the viscosity of the product so that less cocoa butter is needed to obtain the desired fluidity (20).

For preparation of hydrogen peroxide bleached lecithin, 0.05 to 2.0 percent of 35 percent hydrogen peroxide is added to a lecithin emulsion (20 to 50 percent water) at 60 to 94°C and the moisture removed by heating under reduced pressure. Typically, 1.2 percent of hydrogen peroxide solution, 35 percent concentration, is added based on lecithin dry weight (21). The peroxide
TABLE II

Fatty Acid Composition of Soybean Oil, Natural Soybean Lecithin and Oil-Free Soybean Lecithin

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Soybean oil (percent)</th>
<th>Natural lecithin (percent)</th>
<th>Oil-free lecithin (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmitic</td>
<td>10.3</td>
<td>16.4</td>
<td>19.8</td>
</tr>
<tr>
<td>Stearic</td>
<td>4.4</td>
<td>5.9</td>
<td>3.9</td>
</tr>
<tr>
<td>Total saturates</td>
<td>14.7</td>
<td>22.3</td>
<td>23.7</td>
</tr>
<tr>
<td>Oleic</td>
<td>24.5</td>
<td>16.9</td>
<td>9.2</td>
</tr>
<tr>
<td>Linoleic</td>
<td>53.8</td>
<td>54.1</td>
<td>60.2</td>
</tr>
<tr>
<td>Linolenic</td>
<td>7.0</td>
<td>6.8</td>
<td>6.8</td>
</tr>
<tr>
<td>Total unsaturates</td>
<td>85.3</td>
<td>77.8</td>
<td>76.2</td>
</tr>
</tbody>
</table>

Unsaturated/saturated ratio 5.8:1 3.5:1 3.2:1

*Adapted from reference 9. Natural lecithin is the term used by manufacturers to describe separated, unrefined lecithin.
TABLE III

Phosphoglyceride Composition of Crude Safflower Lecithin and Fatty Acid Composition of the Individual Phosphoglycerides

<table>
<thead>
<tr>
<th>Seed type</th>
<th>Phosphoglyceride</th>
<th>Percent Phosphoglyceride</th>
<th>14:0(^b)</th>
<th>16:0(^c)</th>
<th>18:0(^d)</th>
<th>18:1(^e)</th>
<th>18:2(^f)</th>
<th>other</th>
<th>Total unsaturates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilia</td>
<td>PC(^g)</td>
<td>35.9</td>
<td>1.2</td>
<td>14.0</td>
<td>3.7</td>
<td>8.3</td>
<td>72.5</td>
<td>0.3</td>
<td>80.8</td>
</tr>
<tr>
<td></td>
<td>PE(^h)</td>
<td>15.7</td>
<td>0.7</td>
<td>15.6</td>
<td>2.9</td>
<td>5.9</td>
<td>74.6</td>
<td>0.3</td>
<td>80.5</td>
</tr>
<tr>
<td></td>
<td>PI(^i)</td>
<td>26.7</td>
<td>0.9</td>
<td>26.1</td>
<td>5.6</td>
<td>3.5</td>
<td>61.5</td>
<td>2.4</td>
<td>65.2</td>
</tr>
<tr>
<td>Arizona brown stripe</td>
<td>PC</td>
<td>32.0</td>
<td>0.2</td>
<td>13.8</td>
<td>4.1</td>
<td>12.1</td>
<td>68.1</td>
<td>1.7</td>
<td>80.7</td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td>16.2</td>
<td>0.2</td>
<td>19.5</td>
<td>2.9</td>
<td>8.3</td>
<td>69.1</td>
<td>0.0</td>
<td>77.4</td>
</tr>
<tr>
<td></td>
<td>PI</td>
<td>23.0</td>
<td>0.1</td>
<td>29.0</td>
<td>4.8</td>
<td>4.4</td>
<td>59.7</td>
<td>2.0</td>
<td>64.1</td>
</tr>
<tr>
<td>UC-1</td>
<td>PC</td>
<td>39.5</td>
<td>1.4</td>
<td>7.5</td>
<td>0.9</td>
<td>75.9</td>
<td>14.1</td>
<td>0.2</td>
<td>90.0</td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td>13.5</td>
<td>1.0</td>
<td>9.7</td>
<td>0.8</td>
<td>71.2</td>
<td>16.8</td>
<td>0.5</td>
<td>88.1</td>
</tr>
<tr>
<td></td>
<td>PI</td>
<td>20.5</td>
<td>1.4</td>
<td>19.4</td>
<td>4.9</td>
<td>53.7</td>
<td>20.0</td>
<td>0.0</td>
<td>73.7</td>
</tr>
</tbody>
</table>

\(^a\) Adapted from reference 14.
\(^b\) Myristic acid.
\(^c\) Palmitic acid.
\(^d\) Stearic acid.
\(^e\) Oleic acid.
\(^f\) Linoleic acid.
\(^g\) Phosphatidylcholine.
\(^h\) Phosphatidylethanolamine.
\(^i\) Phosphatidylinositol.
value, meq of peroxide per kg of lecithin, of single-bleached lecithin at the time of packaging is 5 to 80, with the typical product being in the range of 20 to 30.

The Food Chemicals Codex (22) describes lecithin as originating from soybeans and to consist chiefly of phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol. Various amounts of other substances such as triglycerides, fatty acids, and carbohydrates may also be present. Refined grades of lecithin may contain any of these components in varying proportions and combinations depending on the type of fractionation used. The Codex describes oil-free lecithin as having most of the triglycerides and free fatty acids removed and containing 90 percent or more of soy phosphatides. Lecithin varies in color from light yellow to brown depending on whether or not it is bleached. Edible diluents such as cocoa butter and vegetable oils often replace soybean oil to "improve functional and flavor characteristics." Food grade lecithin must contain not less than 50 percent acetone-insoluble matter (phosphatides) nor more than 1.5 percent water, 0.3 percent benzene-insoluble material, 3 ppm arsenic, 40 ppm heavy metals (as lead), or 10 ppm lead. Its acid value must not exceed 36. The Codex provides no specifications for bleached lecithins. Although soybean is the most common source of commercial lecithin, lecithin from corn or safflower oil is also considered GRAS (23).

Two constituents of lecithin, choline and inositol, have been previously evaluated by the Select Committee (24,25), and hydrogen peroxide will be evaluated in another report (26).
III. CONSUMER EXPOSURE DATA

A subcommittee of the National Research Council (NRC) surveyed manufacturers by questionnaire concerning the level of addition of GRAS substances to foods in 1970 and estimated the possible average daily intake of these substances by persons in various age groups. Based on information supplied by those manufacturers who reported adding the substance to at least one food product in a food category, a weighted mean was calculated for the usual and maximal percentage addition of the substance to foods in that category. Such weighted means for the usual levels of addition of lecithin and lecithin bleached with hydrogen peroxide to foods by categories are presented in Table IV. Many foods within these categories probably do not contain added lecithin, either bleached or unbleached.

The NRC subcommittee (27) estimated possible average daily intakes of lecithin and lecithin bleached with hydrogen peroxide based on Market Research Corporation of America (Chicago, Ill.) data on mean frequency of eating foods by food category, U.S. Department of Agriculture data on mean portion size of foods in these categories, and the assumption that all food products within a category contain the substance at the level shown in Table IV. Such an assumption is likely to lead to overestimates of intake, and the NRC subcommittee has recognized that in most cases its calculations of possible intakes are overstated, often by a considerable margin.*

In the case of lecithin and lecithin modified with hydrogen peroxide, such estimates for individuals over 2 years of age were 2034 and 513 mg daily, respectively. These estimates are greatly in excess of those provided by an alternative calculation based on the total poundage of lecithin and lecithin bleached with hydrogen peroxide added annually to processed foods (27). The latter data suggest a daily per capita "intake" from lecithin and lecithin bleached with hydrogen peroxide added to food in 1970 of about 92 and 4 mg, respectively (Table V). Although such disappearance data are likely to be somewhat in excess of actual per capita consumption, the Select Committee considers the data in Table V to be reasonable estimates of average intakes.

Table V also provides estimates of the relative amounts of each compound used in 1960 and 1970 in those foods where comparable figures were available. For the period 1960 to 1970, the

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*An explanation for such overstatements is detailed in Section XI, "Significance and Use of Data in Safety Evaluations," of the NRC subcommittee's report (27). The Select Committee finds this explanation reasonable.
TABLE IV

Level of Addition of Lecithin and Lecithin Modified with Hydrogen Peroxide to Foods by Food Category (27)

<table>
<thead>
<tr>
<th>Food category</th>
<th>Lecithin Weighted mean percent</th>
<th>Lecithin modified with hydrogen peroxide Weighted mean percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baked goods, baking mixes</td>
<td>0.12</td>
<td>0.35</td>
</tr>
<tr>
<td>Breakfast cereals</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Grain products such as pastas or rice dishes</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>Fats and oils</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Milk, milk products</td>
<td>1.33</td>
<td>0.06</td>
</tr>
<tr>
<td>Cheese</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>Frozen dairy desserts, mixes</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>Processed fruits, juices, and drinks</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Meat products</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Poultry products</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Fish products</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Processed vegetables, juices</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Soft candy</td>
<td>0.18</td>
<td>0.06</td>
</tr>
<tr>
<td>Sugar, confections</td>
<td>0.34</td>
<td>0.20</td>
</tr>
<tr>
<td>Sweet sauces, toppings, syrups</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Gelatins, puddings, fillings</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Soups, soup mixes</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Snack foods</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Beverages, nonalcoholic</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>Nuts, nut products</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Reconstituted vegetable proteins</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>Gravies, sauces</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Dairy products analogs</td>
<td>1.17</td>
<td>0.39</td>
</tr>
<tr>
<td>Hard candy</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Chewing gum</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>Seasonings and flavorings</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Baby food formulas</td>
<td>0.08</td>
<td></td>
</tr>
</tbody>
</table>

Blanks in the table mean that the substance is not added to the foods indicated; asterisks (****) mean that (a) the substance is used in a processing phase of the foods indicated but residual levels in the final food product are negligible or unknown, (b) the substance is used in the foods indicated but usage levels were not furnished by industry, or (c) the substance is in the foods indicated but the levels were considered to be reported incorrectly (see explanatory notes in Exhibit 50 of reference 27).
TABLE V

Consumption of Lecithin and Lecithin Modified with Hydrogen Peroxide Based on Total Quantity Used Annually in Foods (27)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Relative amounts used(^a) 1970/1960</th>
<th>Total used (1970)(^b) kg</th>
<th>Per capita daily intake(^c) mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lecithin</td>
<td>1.79</td>
<td>6,900,000(^d)</td>
<td>92</td>
</tr>
<tr>
<td>Lecithin modified with hydrogen peroxide</td>
<td>2.34</td>
<td>300,000(^d)</td>
<td>4</td>
</tr>
</tbody>
</table>

\(^a\)Based only on the reports from those respondents to the NRC survey who submitted information for both 1960 and 1970 (27).

\(^b\)Total usage is based on the sum of kilograms used in foods as supplied by NRC and 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.

\(^c\)Based on total consumption 1970 and a U.S. population of 205 million.

\(^d\)A resurvey in 1975 (75) revealed the use of approximately the same amount.
data indicate that there were about 1.8- and 2.3-fold increases, respectively, in the use of lecithin and lecithin modified with hydrogen peroxide.

Phosphatides also occur naturally in the diet; chicken eggs, beef liver, and beef muscle contain 13.7, 16.2, and 3.2 percent phosphatide, respectively, on a dry weight basis (28). Thus, a serving of liver contains about 5 g and one egg about 1.8 g of phosphatides. Whole milk contains about 0.035 percent phosphatides (29). The fatty acid composition and percentage distribution of the various phosphatide components of soybeans would, of course, differ from those of animal sources. Vegetable sources of lecithin occurring naturally in the diet include soybeans, peanuts, sweet corn, whole wheat, and rice (15).

Slover (30) and Marshall et al. (31) determined the phospholipid content of two low-fat diets fed to a group of 21 human volunteers. One diet provided 2000 calories per day, 25 percent of which was from fats, and contained 1.5 g of phospholipid; the other diet providing 2800 calories, contained 35 percent fat, and about 2.5 g phospholipid per day.

The Joint FAO/WHO Expert Committee on Food Additives (32) estimated the average diet provided about 1 to 5 g daily of lecithin. The data shown in Table V indicate that the daily per capita consumption of lecithin added to foods is about 100 mg; this amount is small compared to the phospholipid present naturally in the diet.
IV. BIOLOGICAL STUDIES

Absorption and metabolism

Ingested phosphoglycerides are subject to hydrolysis by intestinal phospholipases, but there is some uncertainty regarding their exact number and specificity. Phospholipase B simultaneously hydrolyzes both fatty acids attached to phosphoglycerides (33). The best characterized phospholipase is phospholipase A₂, which hydrolyzes the fatty acid esterified to the 2 position of the glycerol moiety of the phosphoglyceride. This reaction produces monoacylglycerides, also referred to as lysophosphoglycerides because they promote the lysis of red blood cells. They are also cytotoxic to the other cell types (34). Lysophosphoglycerides can be further degraded by lysophospholipases which hydrolyze the remaining esterified fatty acid (35). The glycerophosphate derivatives produced by this reaction can be further hydrolyzed to glycerophosphate by enzymes such as glycerophosphohydrolase (36). A phospholipase C type enzyme in the pancreas can hydrolyze phosphatidylinositol to form inositol phosphate and diglyceride (37).

Aeryltransferase enzymes present in the intestinal mucosa and other tissues can catalyze the reacylation of lysophosphoglycerides by acyl-CoA. Intracellular phospholipases and acyltransferases participate in monoacyl-diacyl phospholipid cycles which allow for the synthesis of "custom tailored" acyl constituents of phosphoglycerides (33,35). Lysophosphatidylcholine can be formed in the plasma by the transfer of an acyl group from phosphatidylcholine to cholesterol catalyzed by the enzyme lecithin acyltransferase. Individuals lacking this enzyme may develop hyperlipidemia and atherosclerosis at an early age (38,39). An enzyme system from rat liver microsomes can desaturate 1-acyl-2-eicosatrienoyl phosphatidylcholine to 1-acyl-2-arachidonoyl phosphatidylcholine (40). Phosphatidylcholine, phosphatidylinositol, and phosphatidylethanolamine can be synthesized de novo in mammalian systems (33,35). Bloj and Zilversmit (41) have identified two proteins from rat liver which accelerate the transfer of phosphoglycerides from liposomes to mitochondria or erythrocyte ghosts.

Scow et al. (42) administered phosphatidylcholine radio-labeled on the fatty acid, choline, and phosphate moieties to female rats (Hebrew University strain) by stomach tube and measured radioactivity present in thoracic lymph lecithin for 2 hours after feeding. These studies indicated that in rats dietary phosphatidylcholine is hydrolyzed to 1-acylphosphatidylcholine in the intestine, absorbed, and then reacylated to phosphatidylcholine before incorporation into lymph chylomicrons. The phosphate-choline or phosphate-glycerol bonds were apparently not cleaved in the intestine.
Le Kim and Betzing (43) studied the absorption and metabolism of radiolabeled dilinoleylphosphatidylcholine dissolved in soy triglycerides and fed to young, starved Wistar rats. Over 80 percent of the radiolabel was absorbed within 6 hours and more than 90 percent in 24 hours. Six hours after feeding, 1.8 percent of the radiolabel initially present in the choline fraction had been converted to respiratory CO₂ while 7.7 and 25 percent of the radioactivity from the fatty acids attached to the number 1 and 2 carbons, respectively, of the glycerol backbone had been converted to respiratory CO₂. Six to eight hours after dosing, about 30 percent of the radioactivity from the choline group and about 10 percent of the activity from both acyl groups were localized in the liver. The corresponding figures for blood were 8 and 4 percent, respectively. Minor amounts of radioactivity were seen in all tissues analyzed including lung, spleen, kidney, heart, and brain. Analysis of fats isolated from the liver 6 hours after feeding showed that radioactivity originating from the choline fraction of the fed phosphatidylcholine was found only in liver phosphatidylcholine and lysophosphatidylcholine. About 27 to 30 percent of the radioactivity originating from the linoleyl groups was found in liver triglycerides, about 10 to 12 percent in phosphatidylethanolamine, and 54 to 60 percent in phosphatidylcholine. Analysis of the liver phosphatidylcholine showed about 9 times as much radioactivity from the original number 1 position as from the number 2 position.

In addition to dietary lecithin, phosphoglycerides enter the intestine through the bile. Biliary phosphatidylcholine may facilitate intestinal fat absorption. In rats, deprivation of biliary or dietary phosphatidylcholine or choline was associated with lower rates of fat absorption and mucosal protein synthesis (44). Phosphatidylcholine also participates in the biliary excretion of cholesterol which is solubilized within cholesterol-bile salt-phosphatidylcholine micelles (45).

**Acute toxicity**

The Select Committee found no relevant information concerning the acute toxicity of orally administered lecithin.

**Short-term studies**

Davis (46) fed four dogs 5 g per day of commercial soybean lecithin (about 500 mg per kg body weight). After a latent period of 5 days or more, the erythrocyte count of the dogs was gradually reduced. A maximal decrease of about 15 to 20 percent occurred 15 to 25 days after the beginning of lecithin feeding. Lecithin feeding was discontinued after 30 to 60 days and erythrocyte levels returned to normal in the following 10 to 20 days. Daily dosing of four dogs with 8 mg per kg of choline hydrochloride resulted in similar decreases in erythrocyte count. The
investigator speculated that the choline content of the lecithin was responsible for the decrease in erythrocyte count. No other effect of the lecithin administration was noted.

Kesten and Silbowitz (47) fed atherosclerotic diets containing 150 mg cholesterol daily to 23 young adult chinchilla rabbits, divided into three basic groups. In addition to the basic diet, one group received 1 g (500 mg per kg body weight) and another group 5 g (2500 mg per kg body weight) of crude soy lecithin daily. The oil content of the several diets was equalized. The animals were fed the diets for 7 months. Seven of eight rabbits receiving cholesterol alone developed atherosclerosis of the aorta. Only two of eight rabbits in the group receiving 1 g of lecithin and two of seven receiving 5 g of lecithin developed atherosclerotic lesions.

**Long-term studies**

In a 2-year feeding study, a group of 48 male and 48 female Wistar rats was fed a commercial laboratory diet to which 4 percent soybean lecithin (mean intake 1400 mg per kg body weight per day) was added (48). Similar groups of animals were fed the commercial diet containing 2 or 6 percent of a synthetic emulsifier being evaluated as a substitute for soy lecithin; and a control group was fed the commercial diet with no additions. All the groups of animals had access to food and water ad libitum. The food consumption and body weight were measured at 0, 29, 56, and 95 weeks. Over a 2-year period, no significant differences were seen between control and lecithin-fed rats with respect to mortality, food consumption, and body weight, although there was some tendency for food consumption and body weight to be greater in the lecithin-fed group. At the end of the study, no significant differences between the control and lecithin-fed rats were found in the serum values of glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, lactic dehydrogenase, glucose, urea, total protein or albumin. Blood samples taken at 54 weeks showed no significant differences between the lecithin-fed and control rats with respect to hemoglobin concentration, packed cell volume, red cells, reticulocytes, and total and differential leukocyte counts. In addition, there were no significant differences between control and lecithin-fed rats in organ weights, gross or histopathological findings, or incidence of tumor formation, except for an increase in parathyroid hyperplasia, especially in males (9 out of 41 controls examined and 16 out of 39 in the experimental group). The investigators attributed this increase to the increased phosphate intake in the lecithin-fed animals.

Szepsenwol (49), in 1969, fed 4-week-old TM strain mice 5 to 10 mg of lecithin daily (about 250 to 500 mg per kg body weight). The substance was fed once daily mixed with sugar to improve palatability. The mice were bred and their offspring dosed according to the same protocol. The experiment continued
until all the mice became moribund or died. In addition to the control group receiving only laboratory diet, another group of animals received 200 to 250 mg per kg daily of cholesterol. No brain tumors appeared in 188 control animals that were examined. Brain tumors were noted in 18 of 73 animals fed lecithin and in 20 of 80 of the cholesterol group. The Select Committee is aware of no studies which confirm these results. In the study of Brantom et al. (48), already described, no brain tumors were found in any of the 39 animals examined that had been fed lecithin; one glioma was found in the 41 control rats.

Teratogenicity

Groups of 21 to 23 pregnant CD-1 strain mice were given 0, 16, 74, 345, or 1600 mg per kg daily of lecithin (50). The mice were dosed by oral intubation on days 6 through 15 of pregnancy. Cesarean section was performed on day 17. There was no discernible effect of lecithin dosing on nidation, maternal or fetal survival, or number of abnormalities. A similar protocol was followed with groups of 22 to 24 Wistar strain pregnant rats with no teratogenic effects noted. Groups of 10 to 12 pregnant Dutch-belted female rabbits were dosed by oral intubation with 0, 4.8, 22, 100, or 475 mg per kg of lecithin daily on days 6 through 18 of pregnancy. Cesarean section was performed on day 20 of pregnancy. No effect of lecithin was observed with regard to nidation, maternal or fetal survival, or teratogenicity.

Double-bleached lecithin was found not to be teratogenic to developing chick embryos at doses as high as 200 mg per kg (51).

Mutagenicity

Lecithin was not mutagenic to Salmonella typhimurium strains TA-1535, TA-1537, and TA-1538 or Saccharomyces cerevisiae D4 when tested in plate and suspension systems with and without the presence of activation extracts from lung, liver, kidney, and testicular tissues of mice, rats, and monkeys (52).

The mutagen dimethylnitrosamine was reportedly formed in a model system by the reaction of lecithin with sodium nitrite (53). Sodium nitrite (22.8 mmole) dissolved in 15 ml of water was added to a solution buffered at pH 5.6 containing 4.56 mmole of edible soy lecithin, and the mixture stirred at 78°C for 4 hours. The temperature was chosen to mimic conditions found in a smoke house in view of a proposal to add lecithin to bacon slices. Following extraction and analysis, 0.01 mg of dimethylnitrosamine was formed, equivalent to 2.05 mg of dimethylnitrosamine per kg of lecithin. From 0.003 to 1.1 mg of dimethylnitrosamine was formed when other sources of "lecithin" (e.g.: egg, beef) were used under identical reaction conditions (0.7 to 320 mg dimethylnitrosamine per kg "lecithin").
Human exposure

The effects of lecithin feeding on serum lipid levels have been inconsistent, perhaps because of the different dosage levels and treatment periods employed. The effect of orally administered soy lecithin on serum lipid levels was investigated in 12 patients with Frederickson type II hyperlipoproteinemia (54). The patients were given 1.2 g (20 mg per kg) of soy lecithin daily for 10 to 20 weeks. The normal diet of these patients contained an additional 200 to 400 mg of phospholipid (3.3 to 6.7 mg per kg). After 20 weeks on this regimen, 2.4 g of soy lecithin was given daily for 4 months. The patients served as their own controls; blood lipid levels were measured four to five times at weekly intervals before the start of the experiment. Eight of the patients were on a "regular Dutch diet" and four consumed a special "cholesterol-lowering diet." During or after the lecithin treatment at the 1.2 g a day level, there were no significant changes in the serum level of cholesterol, triglycerides, phospholipids, or total lipids. Also, there was no change in the concentration of lipids in the serum β-lipoprotein fraction. At the 2.4 g level, there were small, statistically significant decreases in the serum cholesterol, serum total lipid levels and concentration of lipids in the β-lipoprotein fraction compared with the control period. The authors conclude that these changes were of no "clinical relevance."

Steiner and Domanski (55) fed 25 g of soy lecithin daily for 6 weeks to seven patients and to another patient for 10 weeks. Four of the patients were given a 4-week "control period" and then fed lecithin again for 6 weeks. Six of these patients had coronary arteriosclerosis and the other two patients had rheumatoid arthritis. The lecithin was fed in 5 g portions. During each of the lecithin feeding periods, the serum cholesterol levels declined shortly after lecithin feeding began. About halfway through the feeding period, the serum cholesterol levels declined by an average of 68 mg per 100 ml (range 44 to 144), and then returned to prefeeding levels. The decline was maintained for only 5 weeks despite continuance of the lecithin regimen. Basal metabolic rates during the maximum serum cholesterol depression did not differ from control values.

Adlersberg and Sobotka (56) fed five patients with hypercholesterolemia 12 or 15 g of soy lecithin daily. Striking decreases of about 35 to 70 percent were seen in serum cholesterol values within several weeks and remained depressed during several months of lecithin feeding. Following cessation of treatment, cholesterol levels increased towards the prefeeding level.

Nine male and nine female aged psychiatric patients were fed about 23 g of soy lecithin daily for 90 days (57). Analysis of the serum lipoproteins of these patients showed that the $S_f^{0-12}$ lipoprotein fraction was not affected by lecithin feeding but
the $S_0^f$ 12-20 fraction gradually declined over the first 30 days to about 50 percent of the baseline level before returning to baseline values over the following 60 days of feeding. No sex differences were apparent in the latter two observations, but in females the serum level of $S_0^f$ 12-100 lipoproteins increased about one-third during the 90-day period, while in males this fraction decreased about one-third over the first 60 days and then began rising towards the prefeeding levels.

Effect of lecithin dosing on serum and brain choline and acetylcholine levels

Wurtman et al. (58) measured serum choline values in human volunteers after oral administration of 2.3 g of choline or its lecithin equivalent (100 g). After choline ingestion, serum choline values rose 86 percent above baseline levels within 30 minutes and returned to normal within 4 hours; with lecithin, serum values reached levels of 265 percent of controls in about 4 hours and remained at that level until termination of the experiment, 12 hours after dosing.

In rats, feeding or intraperitoneal injection of choline raised the brain level of acetylcholine (59,60) and variation in the choline content of the animals' diet influenced the concentration of nicotinic acetylcholine receptors in the brain (61). Daily administration of 8 to 20 g of choline to eight patients with Huntington's disease increased choline in cerebrospinal fluid by about 72 percent (62).

Massive oral doses of choline or lecithin produced pharmacological effects in man (63,64). Growdon et al. (64) found that oral administration of 40 to 80 g lecithin daily decreased buccal-lingual-masticatory movements in three patients with tardive dyskinesia.

Effect of injected lecithin

Studies of intravenous administration of lecithin (65-67) are not considered relevant to the safety of the substance as it is used as a food ingredient.

Behavioral studies

Sergeeva (68) determined the effect of lecithin administration on the conditioned reflex activity of groups of eight rats given 5 or 125 mg per kg daily by gavage. The animals were dosed for 3 weeks, then conditioned to light and to the sound of a bell. Electrical shock was the unconditioned stimulus. Compared with controls, the conditioned reflexes developed more quickly in the animals given 5 mg per kg lecithin; by contrast it was not possible to develop a conditioned reflex in the animals given 125 mg
per kg daily. The investigators did not state whether controls were sham-dosed by gavage with a harmless substance. These studies require confirmation.

Bleached lecithin

The Select Committee is not aware of any short- or long-term study where lecithin bleached with hydrogen peroxide was fed to animals. One rat feeding study with hydroxylated lecithin has been reported (69). Both hydrogen and benzoyl peroxide are used in the preparation of hydroxylated lecithin. No ill-effects were noted when the hydroxylated lecithin was fed at 10 percent of the diet for 8 weeks or at 5 percent of the diet for 52 weeks. However, the relevance of this study to bleached lecithin is uncertain because hydroxylated lecithin is prepared under different conditions and has different chemico-physical properties than bleached lecithin. The health aspects of bleaching foods with hydrogen peroxide are considered in another report of the Select Committee (26).

The double bond of the unsaturated fatty acids present in the phosphoglyceride and triglyceride components of lecithin is susceptible to oxidation with the possible formation of hydroperoxides and epoxides. However, there are apparently no studies on the identification of the compounds formed when lecithin is bleached with hydrogen peroxide under conditions similar to those used in the preparation of "food grade" bleached lecithin. In its report on hydrogen peroxide (26), the Select Committee reviews animal feeding studies of peroxides and epoxides of fatty acids. Some harmful effects were observed, but only at very high doses of 250 mg per kg or more. No evidence of carcinogenicity upon oral ingestion was noted. Van Duuren (70) attributed the relative insensitivity of animals to ingested epoxides to their rapid degradation in vivo, especially in the stomach, where acid-catalyzed hydrolysis might be expected. Lipid peroxides are poorly absorbed as such from the intestinal tract, perhaps due to their degradation in the intestinal mucosa (71,72).

Peroxides of methyl oleate and ethyl linoleate were fed to rats at levels of 300 mg per kg daily for 6 weeks with no apparent ill-effects (73). One feeding study carried out in mice and rats indicated that epoxy- and diepoxystearic acid were not carcinogenic when fed for 3 to 5 months daily at doses of 50 to 150 mg per kg body weight (74).
V. OPINION

Food grade lecithin is a complex mixture of substances derived from the processing of soybean, corn, or safflower oil. Almost all of the lecithin of commerce is derived from soybeans. Phosphoglycerides, the major constituents of lecithin, are present throughout the body as chief components of cell membranes; significant amounts are also present in bile and plasma. The major phosphoglycerides found in soy lecithin can be catabolized and also synthesized de novo in mammalian systems. Commercial lecithin may contain up to 35 percent triglycerides; these compounds occur naturally in the diet and are also catabolized and synthesized in man.

The average daily consumption of lecithin added to foods by manufacturers in 1970, based on the total amount reported to be used, was 92 mg, amounting to about 1.5 mg per kg body weight for adults. The corresponding figure for lecithin bleached with hydrogen peroxide was probably less than 4 mg, about 0.07 mg per kg. Thus, the lecithin added to foods amounts to only 2 to 10 percent of the 1 to 5 g of phosphoglycerides consumed daily as natural constituents of the diet.

A 2-year feeding study with rats given 1400 mg lecithin per kg bodyweight daily (equivalent to a human dose of about 84 g daily) showed no adverse effects except for an increased incidence of parathyroid hyperplasia. The parathyroid hyperplasia seen in the rats probably resulted from the increased phosphate load in the diet. No adverse effects have been noted in volunteers taking 20 g or more of lecithin daily for several months.

The Select Committee is not aware of any animal feeding studies with "food grade" bleached lecithin. Similarly, there appear to be no studies identifying the reaction products of lecithin bleached with hydrogen peroxide. However, in another report, the Select Committee reviewed studies of animals fed compounds which conceivably could form as a result of hydrogen peroxide oxidation of unsaturated fatty acids. Limited feeding studies indicate these compounds are not carcinogenic when given orally and are toxic only at doses orders of magnitude greater than could be expected from the addition to food of lecithin bleached with hydrogen peroxide.

No specifications are listed in the Food Chemicals Codex for the peroxide value of lecithin bleached with hydrogen peroxide; the Select Committee believes such specifications should be developed.
In the light of these considerations, the Select Committee concludes that:

There is no evidence in the available information on lecithin and lecithin bleached with hydrogen peroxide 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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