REVIEW OF THE RECENT LITERATURE
ON THE HEALTH ASPECTS OF LECITHIN
AS A FOOD INGREDIENT

1977

Prepared for

BUREAU OF FOODS
FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
WASHINGTON, D.C. 20204

Contract Number FDA 223-75-2090
REVIEW OF THE RECENT LITERATURE ON THE HEALTH
ASPECTS OF LECITHIN AS A FOOD INGREDIENT

1977

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

Contract No. FDA 223-75-2004

by
Michael J. Wade, Ph.D.

LIFE SCIENCES RESEARCH OFFICE
FEDERATION OF AMERICAN SOCIETIES
FOR EXPERIMENTAL BIOLOGY
9650 Rockville Pike
Bethesda, Maryland 20014
FOREWORD

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB) provides scientific assessments of topics in the biomedical sciences. Reports are based upon comprehensive literature reviews and the scientific opinions of knowledgeable investigators engaged in work in specific areas of biology and medicine.

This technical report was prepared for the LSRO Select Committee on GRAS Substances (SCOGS) as a part of their review of the health aspects of using these food ingredients as stipulated in the Food, Drug, and Cosmetic Act for Generally Recognized as Safe substances. Dr. Michael J. Wade prepared the report based on a comprehensive search and evaluative assessment of the current literature in accordance with the provisions of contract no. FDA 223-75-2004. Acknowledgment is made of the assistance of the LSRO staff who provided much of the background information.

Kenneth D. Fisher, Ph. D.
Director
Life Sciences Research Office
<table>
<thead>
<tr>
<th>TABLE OF CONTENTS</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreword</td>
<td>iii</td>
</tr>
<tr>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>I. Chemical Composition of Commercial Soybean</td>
<td></td>
</tr>
<tr>
<td>Lecithin</td>
<td>2</td>
</tr>
<tr>
<td>II. Absorption and Metabolism</td>
<td>5</td>
</tr>
<tr>
<td>III. Long-Term Studies</td>
<td>9</td>
</tr>
<tr>
<td>IV. Special Studies</td>
<td>11</td>
</tr>
<tr>
<td>V. References Cited</td>
<td>15</td>
</tr>
</tbody>
</table>
INTRODUCTION

This report concerns the health aspects of using lecithin as a food ingredient. It reviews the world's scientific literature from 1972 through 1976, and supplements and updates information contained in a scientific literature review (monograph) prepared for FDA by Tracor Jitco, Inc. which summarizes the world's scientific literature up to 1974. To assure completeness and currency as of the date of this report, information has been obtained by searches 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; and by the combined knowledge and experience of members of the LSRO staff.

Lecithin is listed in the Code of Federal Regulations (21 CFR 182.1400) as a miscellaneous and/or general purpose food additive. In this report the term lecithin refers to a particular fraction derived from the processing of vegetable oils and is composed mainly of phosphoglyceride derivatives of glycerol containing a nitrogenous base (Figure 1). Food grade lecithin is currently manufactured only from soybean oil although lecithin obtained from corn or safflower oil would also be considered GRAS. Generally, food grade lecithin is isolated from solvent extracted soybean oil following solvent removal and hydration of the crude oil fraction. The term lecithin has also been used as a synonym for phosphatidylcholine, one of the major phospholipid constituents of food grade lecithin. In this report the term lecithin will be reserved for the food grade phospholipid fraction isolated from vegetable oils, and phosphatidylcholine will be referred to as such. The reader, however, should realize that in the literature the words lecithin and phosphatidylcholine are frequently used interchangeably. A phospholipid fraction from egg yolk is sometimes referred to in the literature as egg lecithin, and phosphatidylethanolamine, an important constituent of lecithin, is sometimes termed cephalin.

It should be recognized that terms such as phosphatidylcholine or phosphatidylethanolamine do not specify discrete chemical entities, since the fatty acids esterified to the 1 and 2 position of the glycerol moiety can vary with respect to chain length and number of double bonds. Thus phosphatidylcholine or any other particular phosphoglyceride may have a variable fatty acid composition depending on its source.

---

\[\text{\textsuperscript{a}}\text{ The document is available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Va., 22161.}\]


\[\text{\textsuperscript{c}}\text{ Letter to LSRO from Bureau of Foods, FDA, dated November 3, 1976.}\]
I. Chemical Composition of Commercial Soybean Lecithin

A recent analysis of a commercial sample of soybean lecithin showed that 82.5 percent of the sample consisted of phospholipids while glycolipids and neutral lipids account for 15 percent and 2.5 percent, respectively (Erdahl et al. 1973). These workers utilized both thin layer and analytical liquid chromatography in their analysis which is given below.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Percent of Sample by Weight&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phospholipids</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>phosphatic acid</td>
<td>7.0 ± 0.8</td>
</tr>
<tr>
<td>unanalyzed phospholipids&lt;sup&gt;c&lt;/sup&gt;</td>
<td>7.9 ± 1.2</td>
</tr>
<tr>
<td>Total phospholipids</td>
<td>82.5</td>
</tr>
<tr>
<td>Glycolipids</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>unanalyzed galactolipids&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3.4 ± 0.7</td>
</tr>
<tr>
<td>Total glycolipids</td>
<td>15.0</td>
</tr>
<tr>
<td>Neutral lipids</td>
<td></td>
</tr>
<tr>
<td>triglyceride</td>
<td>2.0 ± 0.3</td>
</tr>
<tr>
<td>sterols</td>
<td>0.23 ± 0.07</td>
</tr>
<tr>
<td>free fatty acids</td>
<td>0.12 ± 0.01</td>
</tr>
<tr>
<td>unanalyzed neutral lipid&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.15 ± 0.15</td>
</tr>
<tr>
<td>Total neutral lipids</td>
<td>2.5</td>
</tr>
</tbody>
</table>

<sup>a</sup> Adapted from Erdahl et al, 1973.
<sup>b</sup> Mean ± 1 standard deviation
<sup>c</sup> Unanalyzed phospholipids were acylphosphatidylethanolamine, diphasphatidylglycerol, lysophosphatidylethanolamine, lysophosphatidylcholine and unknowns.
<sup>d</sup> The unanalyzed glycolipids were not identified.
<sup>e</sup> Unanalyzed neutral lipid contained diglycerides, monoglycerides, sterol esters, pigments and unknowns.
Figure 1. Structure of the 3 major phosphoglycerides present in lecithin; (a) phosphatidylcholine, (b) phosphatidylethanolamine, (c) phosphatidylinositol. The letter R refers to the side chains of the fatty acids esterified at the numbers 1 and 2 carbon atoms of the glycerol moiety; the numbering scheme of the glycerol carbon atoms is shown in (a).
II. ABSORPTION AND METABOLISM

According to the current lipid bilayer model of cell and organelle membranes, the central portion of the membrane consists of two layers of phospholipids oriented with the fatty acid chains facing one another (White et al., 1973). Thus phospholipids constitute one of the major components of cellular and organelle membranes. For example, phospholipids account for 28 percent of liver microsomal membrane, 32 percent of myelin, and 44 percent of neural microsomal membranes (Albers, 1976). Phosphatidylcholine accounts for 65 percent of the phospholipid in liver microsomal membranes and 22 percent of the phospholipid of myelin. Phosphatidylethanolamine accounts for 20 percent and 36 percent of the phospholipid of liver microsomal membrane and myelin respectively. Phosphoglycerides make up about 0.2 percent of bile fluid, and phosphatidylcholine and other phosphoglycerides are present in plasma at a concentration of about 160 mg per 100 ml. They are found in chylomicra and associated with plasma lipoproteins (White et al., 1973).

Several intestinal enzymes, designated phospholipases, catalyze the breakdown of ingested phosphoglycerides. Phospholipase A₂ (EC 3.1.1.4), a pancreatic enzyme, hydrolyzes the acyl residue esterified to the number 2 carbon of phosphatidylcholine and phosphatidylethanolamine. The products of these reactions are named lysophosphatidylcholine and lysophosphatidylethanolamine because they can cause hemolysis of red blood cells. The structure of lysophosphatidylcholine is shown in figure 2. Some snake venoms contain a phospholipase A₂ which can catalyze the formation of the above two compounds with resulting hemolysis and tissue damage (Oehme et al., 1975). In the intestine lysophosphatidylcholine is a good detergent and an aid in lipid emulsification. Lysophospholipases (EC 3.1.1.5), also present in the intestinal tract, can further degrade these lysophosphoglycerides by cleavage of the acyl group esterified to the number 1 carbon of the glycerol moiety (White et al., 1973). Lysophosphatidylcholine is also formed in plasma by the reaction, catalyzed by the enzyme lecithin acyltransferase (EC 2.3.1.43), in which a cholesterol ester is formed by transfer of the fatty acid group at the 2 position of phosphatidylcholine to the 3 hydroxyl group of cholesterol. However, normally the tissue concentrations of lysophosphoglycerides are so low they are difficult to measure accurately (Portman and Illingsworth, 1974). The subject of phosphoglyceride metabolism was recently reviewed by van den Bosch (1974). There appears to be confusion as to the exact number and specificity of the digestive enzymes responsible for phosphoglyceride metabolism. This is partly due to the fact that these enzymes exhibit different overlapping substrate specificities and reaction rates depending on experimental conditions such as presence of detergents.
Figure 2. Structure of lysophatidylcholine. \( R \) represents the side chain of the fatty acid esterified at the number 1 carbon atom of the glycerol moiety.
Robins (1975) studied the fate of labeled phosphatidylcholine infused into male Sprague-Dawley rats through a duodenal catheter. The common bile duct and terminal ileum of the animals were also cannulated. A solution of phosphatidylcholine labeled with $^{32}P$ and a $^3H$ either on the choline function or on a palmitate residue esterified to the 1 position of the glycerol moiety (see Figure 1) was infused into the animals for 3 hours. The outflow of the bile duct and ileum was collected for 24 hours beginning at the start of phosphatidylcholine infusion. More than 90 percent of the radioactivity of the infused lecithin was absorbed in 24 hours. About 60 percent of the infused lecithin was found to be hydrolyzed in the intestinal lumen after 3 hours of continuous lecithin infusion. Hepatic retention of radioactivity 3 and 24 hours after lecithin administration was much higher for radioactivity derived from choline than from palmitate or phosphate. Only 1.4 percent of the label from palmitate or 0.9 percent of the phosphorus label reappeared in the bile phosphatidylcholine during the 24 hours following dosing. In contrast, 10 percent of the infused radioactivity from choline did reappear in the bile in the 24 hours following dosing. Robins interpreted his results to mean: (1) 99 percent of the biliary phosphatidylcholine represents new synthesis; (2) enterohepatic recycling of intact phosphatidylcholine does not occur; and (3) that absorbed phosphatidylcholine is subject to complete hydrolysis. Robins, however, did not account for all the absorbed radioactivity and it is possible that some intact lecithin was incorporated into tissues other than the liver or was excreted in the urine.

Rodgers et al. (1975) investigated the metabolism of radiolabeled phosphatidylcholine after it was infused via a duodenal catheter into Sprague-Dawley rats. These studies suggested that some of the lysophosphatidylcholine formed in the lumen of the intestine by hydrolysis catalyzed by pancreatic phospholipase $A_2$ can be absorbed without further catabolism and reutilized for phosphatidylcholine synthesis by the jejunum.
III. LONG-TERM STUDIES

In a 2-year feeding study, rats were fed a commercial lab chow diet to which 4 percent soybean lecithin (4 g per kg body weight per day) was added (Brantom et al., 1973). Another group of animals were fed the lab chow diet containing 4 percent of a synthetic emulsifier being evaluated as a substitute for soy lecithin; and a control group of rats were fed the lab chow with no additions. All 3 groups of animals had access to food and water ad libitum. Over a 2-year feeding period, no significant differences were seen between control and lecithin-fed rats with respect to mortality, food consumption and body weight. The food consumption and body weight were measured at 0, 29, 56 and 96 weeks. At the end of the study, no significant differences between the control and lecithin-fed rats were found in the serum values of glutamic-oxaloacetate transaminase, glutamic-pyruvate transaminase, lactic dehydrogenase, glucose, urea or total nitrogen. In addition, there were no significant differences between control and lecithin-fed rats in organ weights, histopathological findings, hematological parameters or incidence of tumor formation.
IV. SPECIAL STUDIES

A. Clinical Studies

The effect of orally administered soya lecithin on serum lipid levels was investigated in 12 Dutch patients with type II hyperlipoproteinemia (ter Welle et al., 1974). The patients were given 1.2 g (20 mg per kg) of lecithin a day for 10 to 20 weeks. The normal diet of these patients contained an additional 200 to 400 mg of phospholipid (3.3 - 6.7 mg per kg). After 20 weeks on this regimen, 2.4 g of soya lecithin were given daily for 4 months. The patients served as their own controls; blood lipid levels were measured four to five times at weekly intervals prior to the start of the experiment. Eight of the patients were on a "normal Dutch diet" and four were on 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 but "clinically unimportant" increases in the serum cholesterol, serum total lipid levels and concentration of lipids in the β lipoprotein fraction.

B. Studies on Atherosclerosis

Altman and colleagues (1974) studied the influence of lecithin administration on the heart and aorta of rabbits made atherosclerotic by feeding of a diet high in lard oil and cholesterol. The rabbits were maintained on the atherosclerotic diet for 6 months. The rabbits were then divided into six groups. The control, group I, was maintained on the atherosclerotic diet; group II was taken off the atherosclerotic diet and maintained on normal lab chow for 3 months. Group III was transferred to the normal lab diet with the addition of 7.5 percent commercial lecithin. Only very scanty details of the effects of lecithin feeding on the animals were reported. All of the above three groups showed extensive atherosclerotic lesions and enlarged, pale livers with fatty degeneration. The authors speculated that the doses of lecithin given may have been too high and actually caused a slight worsening of atherosclerosis rather than a beneficial effect. In addition these workers investigated the effects on atherosclerotic rabbits of twice-weekly intravenous injections of 5 ml of a phosphatidylcholine suspension. Animals were injected with a 10 percent aqueous emulsion of a product consisting of about 95 percent phosphatidylcholine and 5 percent phosphatidylethanolamine dissolved

---

a The commercial lecithin used by Altman et al (1974) was reported to contain 29.5 percent phosphatidylcholine, 29.5 percent phosphatidylethanolamine and 31.6 percent phosphatidylinositol. The remaining 9.9 percent consisted of unspecified amounts of soybean oil, sterols and other unnamed substances.
in an unspecified oily carrier. Group IV was fed the normal diet with twice-weekly injections of the phosphatidylcholine. Group VI, in addition to being given the twice-weekly phosphatidylcholine injections, was continued on the atherosclerotic diet. Group V received twice-weekly phosphatidylcholine injections while on the initial 6-month atherosclerotic diet. Groups IV, V and VI had markedly reduced atherosclerotic lesions as compared to groups I, II and III; atherosclerotic plaques were only present in the aorta region near the heart. No liver abnormalities were noted in groups IV, V and VI and no harmful effects from the treatment were mentioned. These workers reported that early in their work they infused the rabbits with the commercial lecithin and observed toxic, sometimes fatal reactions. The authors did not further describe these toxic reactions.

C. Effect of Lecithin on Fat Absorption

O'Doherty et al (1973) investigated the effects of phosphatidylcholine feeding on fat absorption and mucosal protein synthesis in male Wistar rats with cannulated bile ducts and in sham operated controls. The day after the operation the animals were fed by stomach tube a micellar solution containing 800 mg of monoolein and free fatty acids. Uptake of radiolabeled fatty acid into liver and adipose tissue of the cannulated rats was about 10 percent of that seen in sham operated animals as measured at 2, 4 and 8 hours after feeding. Inclusion of 50 mg phosphatidylcholine (167 mg per kg body weight) or 5 mg choline (16.7 mg per kg body weight) in the fatty meal caused a marked increase in radioactivity in the liver and adipose tissue of the cannulated animals and a small increase in the tissues of the sham operated animals. Five hours after feeding the 800 mg meal, 91 mg of fat was found in the jejunum of the controls and 390 mg in the jejunum of the cannulated animals. Inclusion of choline or phosphatidylcholine in the meal reduced the amount of fat after 5 hours in the jejunum of the cannulated animals to 82 or 87 mg respectively. Inclusion of phosphatidylethanolamine, cholesterol or inositol in the test meal had no effect on jejunal fat clearance. These investigators also found the incorporation of radioactive leucine into protein by rat everted sac jejunum preparations was increased if the animals had been fed choline or phosphatidylcholine prior to sacrifice and preparation of the everted sacs.

Intra-aortic injection of soy-fat emulsion containing lecithin changed the apportionment of radioactive progesterone between subcellular fractions from uterine tissue in pregnant rats (Haukkamaa et al, 1972). Haukkamaa et al. (1972) also performed equilibrium dialysis studies with a purified lecithin fraction from this emulsion, and found that the incubation in vitro of the lecithin fractions with plasma caused release of progesterone bound to the plasma proteins. According to these authors, previous studies showed that injection

a The actual chemical composition of this fraction was not stated by the authors.
of the soya fat emulsion increased myometrial activity in pregnant women and induced labor contractions leading to delivery.

The mutagen dimethylnitrosamine was reportedly formed in a model system by the reaction of lecithin with sodium nitrite (Pensabene et al, 1975). Sodium nitrite (22.8 mmole) dissolved in 15 ml of water was added to a solution buffered at pH 5.6 containing 4.5 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 there were 0.01 mg of dimethylnitrosamine formed (2.05 ppm calculated as mg of dimethylnitrosamine per mg of lecithin). From 1 to 0.03 mg of dimethylnitrosamine were formed when other sources of "lecithin" (egg, beef, etc.) were used under identical reaction conditions.
V. REFERENCES CITED


