EVALUATION OF THE HEALTH ASPECTS OF CELLULOSE AND CERTAIN CELLULOSE DERIVATIVES AS FOOD INGREDIENTS

December, 1973

Prepared for

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

THIS DOCUMENT HAS NOT BEEN APPROVED FOR PUBLIC RELEASE

Contract No. FDA 72-85
EVALUATION OF THE HEALTH ASPECTS OF CELLULOSE AND CERTAIN CELLULOSE DERIVATIVES AS FOOD INGREDIENTS

December, 1973

Prepared for

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

THIS DOCUMENT HAS NOT BEEN APPROVED FOR PUBLIC RELEASE

Contract No. FDA 72 - 85

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) food substances that are being made by the Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology (FASEB) under contract with the Food and Drug Administration (FDA) of the U.S. Department of Health, Education, and Welfare. The Federation recognizes that the safety of GRAS substances is of national significance, and its resources are particularly suited to marshalling the opinions of knowledgeable scientists to assist in these evaluations. The Life Sciences Research Office, established in 1962 to make scientific assessments in the biomedical sciences, is conducting these studies.

Qualified scientists were selected as consultants to make a continuing review, analysis, and evaluation of 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. Members of the Select Committee on GRAS Substances who have contributed to this report are named in Section VII. The Select Committee's evaluations are being made independently of FDA or any other governmental or nongovernmental group.

These reports are approved by the Select Committee prior to submission to FDA. Although most LSRO consultants are members of FASEB constituent societies, the reports do not necessarily reflect the views of the Federation as a corporate body or carry the endorsement of the members of its constituent societies.

C. Jelleff Carr
C. Jelleff Carr, Ph.D., Director
Life Sciences Research Office
FASEB
# CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>II.</td>
<td>Background information</td>
<td>2</td>
</tr>
<tr>
<td>III.</td>
<td>Consumer exposure data</td>
<td>7</td>
</tr>
<tr>
<td>IV.</td>
<td>Biological studies</td>
<td>8</td>
</tr>
<tr>
<td>V.</td>
<td>Opinion</td>
<td>17</td>
</tr>
<tr>
<td>VI.</td>
<td>References cited</td>
<td>21</td>
</tr>
<tr>
<td>VII.</td>
<td>Scientists contributing to this report</td>
<td>26</td>
</tr>
</tbody>
</table>
I. INTRODUCTION

Under terms of FDA Contract 72-85, FASEB's Life Sciences Research Office was requested to evaluate the health aspects of using cellulose and certain cellulose derivatives as food ingredients, primarily on the basis of information contained in a monograph furnished by FDA (1), summarizing the world's scientific literature from 1920 through 1970, and in certain supplemental documents, including current literature citations obtained through Toxline* and Medline*, available as of December, 1973. Cellulose and certain cellulose derivatives are food substances that have been generally recognized as safe (GRAS) under the provisions of Section 121.101 of the Code of Federal Regulations (21 CFR 121.101, revised April 1, 1973).

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321 (s)], GRAS substances are exempt from the requirement of premarketing clearance for food additives. It is stated in 21 CFR 121.1 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. It is recognized further (21 CFR 121.3) that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

The Select Committee on GRAS Substances of LSRO is making its evaluations of these substances in full recognition of the foregoing provisions. In reaching its conclusions on safety the Select Committee, in accord 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, and realizes that a conclusion, based on such reasoned judgment, is expected even in instances where the available information is qualitatively or quantitatively limited. The Committee is also aware that biological testing, like all of science, is dynamic. Accordingly, the Committee's conclusions, based as they are on the

---

*Nationwide online bibliographic retrieval systems initiated by the National Library of Medicine, Bethesda, Maryland.*
information now available, cannot anticipate and be guided by experiments not yet done or by the results of tests that may be reconducted, using new technologies that are continually being evolved. 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 cellulose and certain cellulose derivatives 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

Cellulose is a natural substance normally present in most diets because it is the major structural carbohydrate of green plants. Cellulose is essentially a linear polymer of glucopyranose units connected by β-1, 4-glucoside links. In nature, cellulose is present in plant cell walls as fibers. The molecular weight of isolated cellulose is approximately 50,000. The principal sources of cellulose for food-related purposes are cotton linters and wood pulp (1, 2, 3).

Chemical processing converts cellulose into forms or derivatives suitable for incorporation into food products, or for use in food packaging materials.

The Code of Federal Regulations (4) lists as Generally Recognized as Safe (GRAS) the following cellulose derivatives: methyl cellulose and sodium carboxymethyl cellulose as miscellaneous and/or general purpose food additives; cellulose acetate and ethyl cellulose as substances migrating to food from paper or paperboard products used in food packaging; and carboxymethyl cellulose as a substance migrating to food from cotton or cotton fabrics used in dry food packaging. Hydroxypropylmethyl cellulose is a food additive regulated under 21 CFR 121.1021.

The Code of Federal Regulations (5) also indicates that the food additive hydroxypropylmethyl cellulose may be safely used in food and lists the following cellulose derivatives as substances that may be safely used in cellophane sheets used in food packaging: carboxymethyl-hydroxyethyl cellulose polymer, cellulose acetate butyrate, cellulose acetate propionate, hydroxyethyl cellulose, hydroxypropyl cellulose, and nitrocellulose.
The Food Chemicals Codex (3) provides specifications for food grade preparations of the following cellulose derivatives: microcrystalline cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose, and sodium carboxymethyl cellulose.

Possible daily intake and annual food use data are available (6) for the following cellulose derivatives: cellulose, pure and regenerated (assumed to include microcrystalline cellulose), carboxymethyl cellulose, sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose.

Those derivatives that are included in the GRAS list and for which the Select Committee has adequate information, are considered in this report. In addition, cellulose and some cellulose derivatives that are used in food but are not included in the GRAS list, are also considered where the available information warrants. Specifications for the cellulose derivatives for which this information is available, are given in Table I.

Microcrystalline cellulose is purified, partially depolymerized cellulose prepared by treating α-cellulose, obtained as a pulp from fibrous plant material, with mineral acids (2, 3). It occurs as a fine, white, odorless microcrystalline powder used to convert liquid foods to granular forms or smooth-spreading gels, and as an anticaking or binding agent.

Methyl cellulose is made from cotton linters or wood pulp by treatment with alkali and methyl chloride. Methoxyl groups are formed with a possible substitution ratio of three per anhydroglucopyranose unit. Superior physical properties for food use are obtained with lower degrees of substitution providing from 27.5 to 31.5 percent methoxyl content in the dried methyl cellulose (2, 3). Methyl cellulose is used as a thickener, stabilizer, emulsifier, bodying or bulking agent, and binder in foods. It was first used in foods in the United States in 1960 (6).

Sodium carboxymethyl cellulose is produced by treating wood pulp or cotton linters with alkali and monochloracetic acid. It occurs as a white or cream colored powder or granules (2, 3). For food use, the optimum degree of substitution of a carboxymethyl residue on each anhydroglucopyranose unit of cellulose is 0.95. By preliminary mild acid hydrolysis, the degree of polymerization (i.e., molecular size) of the cellulose may be reduced before carboxymethylation. Control of the degree of substitution and the degree of polymerization during processing, results in production of a wide variety of derivatives that
<table>
<thead>
<tr>
<th>Product</th>
<th>Composition</th>
<th>Limits of impurities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Arsenic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ppm</td>
</tr>
<tr>
<td>Cellulose, pure and regenerated</td>
<td>None specified</td>
<td>†² 3</td>
</tr>
<tr>
<td>(including micro-crystalline cellulose)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methyl cellulose³</td>
<td>Not less than 27.5 percent and not more than 31.5 percent methoxyl groups</td>
<td>†³ 3</td>
</tr>
<tr>
<td>Sodium carboxymethyl cellulose³</td>
<td>Not less than 99.5 percent sodium carboxymethyl cellulose</td>
<td>†³ 3</td>
</tr>
<tr>
<td>Hydroxypropylmethyl cellulose</td>
<td>Minimum of 3 percent, maximum of 12 percent hydroxypropoxy1 groups; minimum of 19 percent, maximum of 30 percent methoxyl groups</td>
<td>†³ 3</td>
</tr>
<tr>
<td>Ethyl cellulose³</td>
<td>Not less than 44 percent and not more than 50 percent ethoxyl groups</td>
<td>†³ 3</td>
</tr>
<tr>
<td>Cellulose acetate³</td>
<td>None specified</td>
<td>--</td>
</tr>
</tbody>
</table>

¹ Expressed as lead  
² † = Not more than  
³ On the GRAS list
differ in such physical properties as gelling, temperature, viscosity, and dispersibility in water. Sodium carboxymethyl cellulose is used as a thickening agent and stabilizer in foods. Because carboxymethyl cellulose is spontaneously converted to the sodium salt in alkaline solution, it is probable that any distinction between carboxymethyl cellulose and sodium carboxymethyl cellulose in foodstuffs is artificial. In much of the literature, no distinction is made between the two; in this report the terms carboxymethyl cellulose and sodium carboxymethyl cellulose are used interchangeably, unless otherwise noted. Both were first used in foods in the United States in 1945 (6).

Hydroxypropylmethyl cellulose is synthesized from methyl cellulose by the action of alkali and propylene oxide. The resultant product is a water soluble ether derivative of cellulose containing both methoxy and hydroxypropyl groups. The degree of substitution is 1.08 to 1.83 with the hydroxypropyl groups as the minor constituent (2,7). It is used as a thickening agent, stabilizer, and emulsifier.

Ethyl cellulose is synthesized from wood pulp or cotton linters by treatment with alkali and ethyl chloride. The degree of substitution of ethoxyl groups is 2.6 representing from 44 to 50 percent of the dry weight. Ethyl cellulose is essentially insoluble in water in contrast to methyl cellulose, but more soluble than methyl cellulose in non-polar solvents (3). It is used as a protective coating component of vitamin preparations, as a binder and filler, and as a component of paper and paperboard food packaging materials.

Data on the percentages added in various foods of cellulose and those cellulose derivatives for which information is available, are summarized in Table II.

Table III contains information provided by a National Research Council subcommittee (6) on the quantity of cellulose and three of its derivatives reported to be used in food products in 1970, together with possible per capita intakes calculated from these figures. Other NRC data (6), not tabulated in Table III, give a rough indication of trends in food use of several cellulose derivatives between 1960 and 1970. They show that in this period, the use of methyl cellulose doubled; the use of carboxymethyl cellulose increased 13-fold; and the use of sodium carboxymethyl cellulose declined slightly.
**TABLE II**

Percentages of Cellulose and Several Cellulose Derivatives Added to Foods (6)

<table>
<thead>
<tr>
<th>Food category</th>
<th>Cellulose, pure and regenerated (including microcrystalline cellulose)</th>
<th>Methyl cellulose*</th>
<th>Carboxymethyl cellulose*</th>
<th>Sodium carboxymethyl cellulose*</th>
<th>Ethyl Cellulose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baked goods, baking mixes</td>
<td>4.83</td>
<td>29.00</td>
<td>0.15</td>
<td>0.36</td>
<td>0.12</td>
</tr>
<tr>
<td>Other grain products, pastes</td>
<td></td>
<td></td>
<td>0.75</td>
<td>1.00</td>
<td>0.01</td>
</tr>
<tr>
<td>Fats and oils</td>
<td>3.00</td>
<td>4.50</td>
<td>0.07</td>
<td>0.12</td>
<td>0.60</td>
</tr>
<tr>
<td>Milk, milk products</td>
<td>0.25</td>
<td>0.39</td>
<td>0.02</td>
<td>0.04</td>
<td>0.05</td>
</tr>
<tr>
<td>Cheese</td>
<td>1.00</td>
<td>1.00</td>
<td>0.40</td>
<td>0.40</td>
<td>0.08</td>
</tr>
<tr>
<td>Frozen dairy desserts, mixes</td>
<td>0.40</td>
<td>0.85</td>
<td>0.41</td>
<td>0.46</td>
<td>0.01</td>
</tr>
<tr>
<td>Processed fruits, juices and drinks</td>
<td></td>
<td></td>
<td>0.08</td>
<td>0.08</td>
<td>0.06</td>
</tr>
<tr>
<td>Fruit ices, water ices</td>
<td></td>
<td></td>
<td>0.07</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Meat products</td>
<td>0.94</td>
<td>1.41</td>
<td>0.04</td>
<td>0.07</td>
<td>0.06</td>
</tr>
<tr>
<td>Poultry products</td>
<td>2.00</td>
<td>3.00</td>
<td>0.01</td>
<td>0.02</td>
<td>0.36</td>
</tr>
<tr>
<td>Eggs, egg products</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Fish products</td>
<td>2.50</td>
<td>3.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Processed vegetables, juices</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.20</td>
<td>0.66</td>
<td>0.07</td>
</tr>
<tr>
<td>Candy, soft</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.10</td>
</tr>
<tr>
<td>Sugar, confections</td>
<td>0.40</td>
<td>0.68</td>
<td>0.25</td>
<td>0.25</td>
<td>0.14</td>
</tr>
<tr>
<td>Jams, jellies, sweet spreads</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td>Sweet sauces, toppings, syrups</td>
<td>0.90</td>
<td>1.03</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.07</td>
</tr>
<tr>
<td>Gelatins, puddings, fillings</td>
<td>0.75</td>
<td>1.00</td>
<td>0.20</td>
<td>1.00</td>
<td>0.06</td>
</tr>
<tr>
<td>Soup, soup mixes</td>
<td>0.35</td>
<td>0.75</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Beverages Type I (nonalcoholic)</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Nuts, nut products</td>
<td>0.54</td>
<td>0.54</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Gravies, sauces</td>
<td>0.75</td>
<td>1.00</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.22</td>
</tr>
<tr>
<td>Dairy products analogs</td>
<td>0.52</td>
<td>1.25</td>
<td>0.15</td>
<td>0.20</td>
<td>0.23</td>
</tr>
<tr>
<td>Hard candy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Chewing gum</td>
<td>2.20</td>
<td>2.20</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*On the GRAS list*
Table III

Consumption of Cellulose and Certain Cellulose Derivatives Based on Total Quantity Used in Foods (6)

<table>
<thead>
<tr>
<th>Derivative</th>
<th>Quantity used in foods, 1970$^1$</th>
<th>Intake calculated from quantity used$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>kg</td>
<td>mg/person/day</td>
</tr>
<tr>
<td>Cellulose, pure and regenerated (including microcrystalline cellulose)</td>
<td>438,526</td>
<td>5.7</td>
</tr>
<tr>
<td>Methyl cellulose$^3$</td>
<td>89,689</td>
<td>1.2</td>
</tr>
<tr>
<td>Carboxymethyl cellulose$^3$</td>
<td>499,654</td>
<td>6.5</td>
</tr>
<tr>
<td>Sodium carboxymethyl cellulose$^3$</td>
<td>2,823,935</td>
<td>36.8</td>
</tr>
</tbody>
</table>

$^1$ Recalculated to 100 percent from NRC poundage data which they estimate to be about 60 percent of the total poundage used (6).

$^2$ Based on the quantities indicated in Column 2 and a U.S. population of 210 million.

$^3$ On the GRAS list.

III. CONSUMER EXPOSURE DATA

The National Research Council subcommittee has supplied the data given in Table IV on the possible daily human intake of cellulose and several cellulose derivatives in the total diet, by individuals in various age groups (6). The Select Committee has converted these figures to possible intakes per kilogram of body weight.

It is recognized that the figures calculated for the daily intake of cellulose and cellulose derivatives per kg of body weight in the age group
TABLE IV

Possible Daily Intake (6)

<table>
<thead>
<tr>
<th>Total intake, mg</th>
<th>Intake, mg per kg body weight*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AGE</td>
</tr>
<tr>
<td>238.9</td>
<td>1097.0</td>
</tr>
<tr>
<td>16.7</td>
<td>48.8</td>
</tr>
<tr>
<td>17.2</td>
<td>45.5</td>
</tr>
<tr>
<td>23.4</td>
<td>48.9</td>
</tr>
<tr>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*Calculations based on an average weight of 60 kg for an adult (8) and the following estimated weights of infants by age groups: 0-5 mos., 5 kg; 6-11 mos., 8 kg; and 12-23 mos., 11 kg (9).

**On the GRAS list
2-65+ years could be deceptively low, since the majority of individuals from age 2 to maturity will probably weigh less than 60 kg. However, such deviations from the figures in the table must also be considered in respect to total production and use of cellulose and its derivatives. The National Research Council subcommittee has pointed out that its calculations of intakes in most cases are overstated, often by considerable margins.* That these human intakes are undoubtedly overstated is demonstrated by the figures given in Table III which show intakes of cellulose and some cellulose derivatives calculated from the total amounts reported to be used for food purposes in the United States in 1970.

On the basis of a comparison between Tables III and IV, the Select Committee regards the figures in Table IV, with the exception of those for cellulose, as levels that are not likely to be achieved by any of the age groups. Such levels for cellulose might be achieved or exceeded if the cellulose of natural origin were to be added to the estimates of cellulose added to foods.

IV. BIOLOGICAL STUDIES

The evidence suggests that orally administered cellulose and its derivatives pass unchanged through the gastrointestinal tracts of rats and man. For this reason few LD₅₀ values have been reported; however, one figure of 27 g per kg has been reported as the oral LD₅₀ in white rats fed sodium carboxymethyl cellulose (10). Because the fate of orally ingested cellulose and cellulose derivatives has been studied extensively, pertinent data for each substance are considered separately.

A. CELLULOSE, MICROCRYSTALLINE CELLULOSE

Metabolism: Four rats fed ¹⁴C-labeled microcrystalline cellulose at 10 and 20 percent in the diet excreted 96 to 104 percent of the ¹⁴C-label in the feces. One human subject received 150 g of ¹⁴C-labeled microcrystalline cellulose on one day and 150 g of unlabeled material daily for the subsequent 10 days. No radio-

*An explanation for such overstatements is detailed in Section XI, "Significance and Use of Data in Safety Evaluations," of the NRC subcommittee's report (6). 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 of the intake of substances used in food processing, food consumption data collected specifically for this purpose are needed."
activity was found in the urine or respiratory CO$_2$. Complete recovery of the radioactive label was found in the feces in two days (11).

It has been demonstrated that when proper precautions are observed, no significant breakdown of microcrystalline cellulose takes place in passage through the human gastrointestinal tract. Microscopic examination of samples of feces collected after 5½ weeks supplementation of free-choice diets of 2 human subjects with 30 g microcrystalline cellulose daily showed no change in the cellulose particles recovered in the feces. Microcrystalline cellulose was fed to one subject in the dry flour form and in the colloidal gel form to the other. As recovered from the feces, the cellulose particles had completely normal and definitive birefringence patterns indicative of no significant chemical or physical breakdown within the body. However, quantitative recovery data were not reported (12).

**Acute and short term data:** Single oral doses of a refined form of $\alpha$-cellulose (Cellan 300), up to 3,160 mg per kg in male albino rats, produced no acute deaths (13). Autopsies 7 days later showed no pathological effects. Microcrystalline cellulose, 30 g per day, was added to the free-choice diet of 16 humans for a 6-week period (14). No pathological changes were found in blood and urine samples. A similar study, over a two-week period in eight humans produced similar results (15).

**Long-term data:** Groups of 100 rats were fed diets of 30 percent dry, gel, or fibrous forms of cellulose for 72 weeks (16). The gel diet resulted in more weight gain than controls during the first year, but there were no differences in appearance, behavior, food consumption, or survival in the two groups. Terminal body weights and heart weights of females, and liver weights of males on the gel diet, were lower than controls. Changes were observed in the kidneys of females, especially in the dry and gel groups, but the kidneys of the male rats were normal. Dystrophic calcification of the terminal proximal tubules was found in some kidney specimens from female rats, but this was not related to the ingestion of the cellulose. All other organs were normal.

**Reproduction studies:** In rats maintained on 30 percent microcrystalline cellulose for 3 generations, second and third generation litters showed adverse effects on reproduction (17). The indices of fertility, live births, and lactation were depressed. No deformities of pups were seen. The adverse effects were attributed to nutritional deficiencies rather than to direct effects of cellulose.
B. METHYL CELLULOSE

Metabolism: Virtually 100 percent of methyl cellulose (Methocel HG) was recovered within 96 hours from the feces of 11 human subjects fed 3 to 8.9 g and three subjects fed 10 g (18). The possibility of methanol or formic acid formation by hydrolysis and oxidation of methyl cellulose in the gastrointestinal tract was considered and shown to be negligible (19).

Acute and short term data: Feeding 2 percent methyl cellulose to chicks for 20 days did not alter their growth rate (20, 21).

Rats fed methyl cellulose, 0.5 g per kg, daily for 4 weeks had no changes in behavior, appetite, or body weight gain (22). A diet containing 10 percent methyl cellulose was fed to rats for 95 days (23). The average intake was 11.4 g per kg per day. No change in growth rate of males occurred, but females showed a 14 percent decrease in growth rate, apparently due to decreased food intake. No pathological changes were found at autopsy of males or females. Other studies extending over 6 months and 8 months produced similar results (24, 25).

Dogs fed methyl cellulose at levels from 0.1 to 100 g per day for 30 days showed no toxic or otherwise undesirable effects (22, 26).

Six normal adult human subjects taking up to 12 g per day of methyl cellulose for one week or more, and 30 patients taking up to 18 g per day, reported relief of constipation, without toxic effects (27). In a similar study, methyl cellulose in doses of 1 to 6 g per day was effective in relieving constipation in a majority of 37 patients. Continual use for as long as eight months did not cause unpleasant or toxic signs (28).

Long term data: Male and female rats were fed diets containing up to 5 percent methyl cellulose for 12, 18, and 24 month periods (29). No significant changes were found in appearance, behavior, growth, mortality, tumor growths, or food intake, or in hematologic studies. Gross and microscopic examinations of the important viscera were negative.

Reproductive and other studies: Three generations of rats maintained on a 5 percent methyl cellulose diet reproduced normally. The methyl cellulose-fed animals had a greater increase in body weight than did the controls (26). In another
study, rats raised on a diet of 5 percent methyl cellulose were mated after eight months. The young were placed on a 5 percent methyl cellulose diet and later mated. All generations had normal, healthy offspring with normal growth rates (30). Gibson et al. (31), fed 0.25 to 0.5 percent methyl cellulose diets daily to pregnant rabbits (day 9 through day 16 of gestation) and observed no teratologic effects but found evidence of fetal toxicity.

Teratologic studies have been made on pregnant mice, rats, and hamsters following the oral administration of large doses of methyl cellulose (Methocel) in corn oil (32). Intubation of daily doses up to 345 mg per kg from day 6 through day 15 of gestation in mice had no clearly discernible effect on nidation or on maternal or fetal survival. The abnormalities observed did not differ from those occurring spontaneously in sham-treated control mice. Doses of 1600 mg per kg per day caused a significant increase in mortality in treated dams and a decrease in the pregnancy rate of survivors. Among the females examined at term, there was a marked increase in the number of resorption sites. The live fetuses were smaller and exhibited significant retardation in maturation. While no clear evidence of a teratologic effect caused by the methyl cellulose could be demonstrated, the findings resembled those produced by high-molecular-weight polysaccharides such as the vegetable gums. The report notes that in the opinion of the investigator, "the administration of what amounts to essentially an LD₅₀ dose (even though distributed over a 10-day period) had resulted in a predictable effect on both the pregnant animal and on the embryos present in the uterus" (32).

Similar studies on rats, with oral doses up to 1320 mg per kg for 10 consecutive days, had no clearly discernible effect on nidation or on maternal or fetal survival (32). The incidence of abnormalities in soft or skeletal tissues was the same in test animals and in sham-treated control rats.

The oral administration of methyl cellulose to pregnant hamsters in doses up to 1000 mg per kg for five days (day 6 through day 10 of gestation) did not produce significant effects on nidation or on maternal or fetal survival. The incidence of abnormalities in soft or skeletal tissues was the same for both treated and control animals (32).

In rats on low vitamin diets, methyl cellulose, in doses of 50 mg per rat, did not decrease absorption of water-soluble or oil-soluble vitamins (33).
Application of 1 or 2 percent methyl cellulose solution to the eyes of rabbits did not produce irritation, and 0.1 and 1 percent solutions did not change the normal contractions of isolated rabbit intestinal strips (22).

C. CARBOXYMETHYL CELLULOSE

Metabolism: Carboxymethyl cellulose passed through the digestive tracts of rats and man unchanged (34).

Acute and short-term data: Single oral doses of 5 g per kg of carboxymethyl cellulose fed to rats, guinea pigs, and rabbits produced no discernible toxic effects, and autopsy after two weeks revealed no gross or microscopic lesions (35). Rats maintained for eight months (35) or for one year (36) on a basal diet, with or without 5 percent carboxymethyl cellulose, did not show differences in food and water intake or in gross or microscopic histologic findings. A similar study with 20 percent carboxymethyl cellulose for 63 days resulted in negative findings (35). Young 100 g male rats fed a hypercholesterolemic diet with 5 percent carboxymethyl cellulose for 8 to 14 days had lower plasma and liver cholesterol levels than control animals (37). The mechanism of the effect was obscure because carboxymethyl cellulose did not alter cholesterol absorption from the gut.

Long-term data: A 5 percent carboxymethyl cellulose diet was fed to weanling mice throughout their lifetime. No differences from controls were observed in food and water intake and body weight, or in gross signs at autopsy (36).

No irritation was produced by application of carboxymethyl cellulose (concentration unstated) to shaved bellies of rabbits five times a week for four weeks (35).

Reproductive studies: Kimmel et al. (38) observed an increase in resorption rate and malformed fetuses in pregnant rats fed 5 ml of a 0.2 percent solution of carboxymethyl cellulose on the eleventh day of gestation.

D. SODIUM CARBOXYMETHYL CELLULOSE

Metabolism: In three studies, all orally administered, sodium carboxymethyl cellulose was recovered in the feces of rats (11, 34, 39). The derivative was also totally excreted by two dogs fed 20 g on each of six days (40).
Acute and short-term data: Single oral doses of 3 g per kg of sodium carboxymethyl cellulose to rats, guinea pigs, and rabbits caused no toxic effects. In addition, rats fed 20 percent sodium carboxymethyl cellulose for 63 days, demonstrated no significant ill effects (35). Rats fed sodium carboxymethyl cellulose (either 0.5 or 1.0 g per kg per day) for six months did not change in weight gain or reproduction as compared to controls; all gross and microscopic findings were negative (10). Five percent sodium carboxymethyl cellulose fed to rats for eight months caused no ill effects (35) and rats fed up to 0.5 g per day for two months did not exhibit signs of toxicity (41).

Guinea pigs were fed either 0.5 or 1.0 g per kg per day of sodium carboxymethyl cellulose for six months or one year (10). There were no differences from control animals in weight gain, fertility, or gross or microscopic findings.

Dogs receiving either 0.5 or 1.0 g sodium carboxymethyl cellulose orally per day for six months were comparable to control animals (10).

Sodium carboxymethyl cellulose was used as a laxative by 128 adult subjects at a dose of 2 to 12 g daily. Laxation was established in most cases in one to three days. No serious effects occurred, although about 15 percent complained of cramps, belching, gas, or fullness of the stomach (42). In another study, 22 adults took about 10 g daily of sodium carboxymethyl cellulose for six months. Seven reported diarrhea or abdominal discomfort; however, no significant hematologic changes, no toxic effects, or significant mucosal irritation were observed (43).

Long-term data: Mice were fed diets of 1 or 10 percent sodium carboxymethyl cellulose for 100 weeks. The body weights and mortalities were similar to control animals. In the same study, rats were fed diets containing 1 percent or 10 percent sodium carboxymethyl cellulose for 104 weeks. Some suppression of body weight occurred in the latter group in both males and females. Hematologic findings and tumor frequency were within normal limits (44).

Sodium carboxymethyl cellulose has been reported to be effective in mice, rats, and dogs as a colloidal laxative (45). It was used as a colloidal laxative in 250 adult human subjects over a three-year period, in doses from 2 to 18 g twice a day, without toxic effects (46).
Reproductive and other studies: Rats were placed on diets containing 0.1, 0.5, or 1 g sodium carboxymethyl cellulose per kg for 25 months. Offspring through the third generation were fed the same diets with no effects on weight gain or gross or microscopic pathology (10).

No irritation was produced by application of sodium carboxymethyl cellulose (concentrations unstated) to the skin of rabbit bellies five times per week for four weeks (35). In human subjects, application of 5 g sodium carboxymethyl cellulose by vaginal instillation in 134 cases caused no irritation to vaginal mucosa or external genitalia (10).

E. HYDROXYPROPYLMETHYL CELLULOSE

Acute and short-term data: Single oral doses in rats of hydroxypropylmethyl cellulose up to 4 g per kg did not cause signs of injury (47). In another study, male and female rats were given hydroxypropylmethyl cellulose (Methocel 70 HG*) as a dietary supplement in levels from 0.3 to 20 percent for 90 days. At the 0.3 and 3 percent dose levels, gross and microscopic examinations were negative; at the 10 percent dose level, slight growth retardation occurred; and at the 20 percent dose level, 30 percent of the rats died of undetermined causes. No histopathological effects related to hydroxypropylmethyl cellulose were found in any animals (48). A similar study of four months' duration, using various proportions of hydroxypropylmethyl cellulose (Methocel 2602) up to 30 percent of the diet, resulted in the death of half the rats only at the highest level of 30 percent of the diet (49). However, in other studies, Methocel 90 HG has been fed to rats up to 20 percent of the diet for three months without ill effects (48); and Methocel 65 HG as either 20 percent or 25 percent of a test diet with no detrimental effects other than some decrease in growth rate (47).

Rats were fed Methocel 65 HG for 30 days at a 10 or 20 percent concentration in the diet. Their body weights were maintained and no pathology was found (47).

*HG denotes "high gel"; the figure preceding refers to temperature of gelling.
A dog fed 25 g per day of Methocel 65 HG for 30 days showed no changes. A dog fed 50 g per day for 30 days lost weight and became anemic. Other findings were normal (47).

Single oral doses of hydroxypropylmethyl cellulose (Methocel HG) up to 8.9 g in human subjects produced only minor side effects (18).

Long-term data: Groups of 100 rats were placed on diets containing 0, 1, 5, and 20 percent hydroxypropylmethyl cellulose for a two-year period. Male rats on the 20 percent diet alone show growth retardation. Blood and urine analyses and mortality rates were not different from controls. Autopsies revealed no abnormalities. The tumor incidence was similar in all groups (47).

Dogs were fed Methocel 65 HG at 0.1, 0.3, 1, or 3 g per kg per day for one year. Their body weights were maintained, and gross and microscopic findings were normal (47).

F. ETHYL CELLULOSE AND CELLULOSE ACETATE

Rats given ethyl cellulose in a 1.2 percent concentration in the diet for eight months had an average daily intake of 182 mg of ethyl cellulose. No changes were observed in food or water intake and there were no gross or microscopic histologic findings of pathologic significance (25).

No biological information is available on cellulose acetate.
V. OPINION

Cellulose is a major constituent of many foods of plant origin. As such it is a significant portion of the diet, but is neither degraded nor absorbed. Cellulose derivatives considered in this report are virtually unabsorbed and little or no degradation of absorbable products occurs in the human digestive tract. In man, consumption of large amounts appears to have no effect other than providing dietary bulk, reducing the nutritive value of such foodstuffs and possibly exerting a laxative effect. However, the existence of certain data and the different categorization of cellulose and the several cellulose derivatives on the GRAS list suggest that the Select Committee should render a separate opinion on each substance considered in this report.

A. CELLULOSE, MICROCRYSTALLINE CELLULOSE

Although pure cellulose and regenerated cellulose, including microcrystalline cellulose are not on the GRAS list, there is nothing in the available information to suggest that such forms of cellulose have significantly different biological properties that distinguish these forms of cellulose from those currently considered as GRAS or from naturally occurring cellulose.

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

There is no evidence in the available information on pure and regenerated cellulose, including micro-crystalline cellulose, 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 future.

B. METHYL CELLULOSE

In humans, virtually 100 percent of orally ingested methyl cellulose can be recovered in the feces within four days, indicating that absorption does not occur. However, in pregnant mice, very high doses of methyl cellulose, while not teratogenic, cause a significant increase in maternal mortality and retardation of fetal maturation. Such increased maternal and fetal toxicity does not occur at a dose of methyl cellulose which is 26-fold (or more) greater than that estimated to be the average daily adult dietary intake. It is noteworthy in this regard that similar toxic effects have been observed in identical tests performed by the same
investigators on a large number of other polysaccharides fed at very high doses. The relative sensitivity of the several animal species to these effects varies, depending on the particular polysaccharide tested, but in all cases very large doses are required. Until these effects have been adequately explained, it appears to be inappropriate to conclude that unrestricted use of such substances in food would be without hazard.

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

There is no evidence in the available information on methyl cellulose that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when it is used at levels that are now current and in the manner now practiced. However, it is not possible to determine, without additional data, whether a significant increase in consumption would constitute a dietary hazard.

C. CARBOXYMETHYL CELLULOSE

Carboxymethyl cellulose is converted spontaneously to a salt in alkaline solution, and it is probable that the distinction between carboxymethyl cellulose and its salts is artificial. However, carboxymethyl cellulose is listed as GRAS as a substance migrating to food from cotton or cotton fabrics used in dry food packaging, while its sodium salt is listed as GRAS as a miscellaneous or general purpose food additive.

In view of the separate listing of carboxymethyl cellulose, the Select Committee concludes that:

There is no evidence in the available information on carboxymethyl cellulose that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when it is used in dry food packaging materials originating from cotton or cotton fabrics as now practiced or as it might reasonably be expected to be used for such purposes in future.

D. SODIUM CARBOXYMETHYL CELLULOSE

Despite the probable lack of distinction between sodium carboxymethyl cellulose and its parent compound, carboxymethyl cellulose, only the sodium carboxymethyl cellulose is GRAS as a miscellaneous and general purpose food additive. As such, there are no data that suggest
it reacts differently than pure and regenerated cellulose or carboxymethyl cellulose.

In view of the foregoing the Select Committee concludes that:

There is no evidence in the available information on sodium carboxymethyl cellulose that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when it is used at levels that are now current or that might reasonably be expected in future.

E. HYDROXYPROPYLMETHYL CELLULOSE

Hydroxypropylmethyl cellulose is not listed as GRAS. It is a food additive used as a thickening agent, stabilizer and emulsifier. Hydroxypropylmethyl cellulose is synthesized from methyl cellulose by the action of alkali and propylene oxide. There are no data available to suggest that hydroxypropylmethyl cellulose possesses adverse health effects; however, teratology studies similar to those conducted with methyl cellulose are not available for its hydroxypropyl derivative. Therefore, it is suggested that, in due course, appropriate studies should be conducted with hydroxypropylmethyl cellulose.

The Select Committee has weighed the foregoing and concludes that:

There is no evidence in the available information on hydroxypropylmethyl cellulose that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when it is used at levels that are now current and in the manner now practiced (21 CFR 121.1021).

F. ETHYL CELLULOSE AND CELLULOSE ACETATE

There is a paucity of data concerning possible adverse health effects of ethyl cellulose and cellulose acetate. Both are included in the GRAS list as substances migrating to food from paper or paperboard products used in food packaging. According to the NRC survey (6), very small amounts of ethyl cellulose also appear to be used in hard candy and chewing gum. In the GRAS context, the quantity of ethyl cellulose or cellulose acetate migrating to foods from packaging would be orders of magnitude below the levels of cellulose and cellulose derivatives now known to occur in foods.
In the light of the foregoing, the Select Committee concludes that:

There is no evidence in the available information on ethyl cellulose and cellulose acetate that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used in food packaging materials as now practiced or as they might be expected to be used for such purposes in future.
ADDENDUM

Since the Select Committee on GRAS Substances submitted its report, "Evaluation of the Health Aspects of Cellulose and Certain Cellulose Derivatives as Food Ingredients" to FDA in December, 1973 it has come to our attention that one of the substances discussed, carboxymethyl cellulose, is presumed by FDA to be GRAS but unpublished as well as GRAS under 21 CFR 121.101(i). Therefore, the Select Committee on GRAS Substances now submits this addendum to be included in its December, 1973 report to clarify the conclusions concerning both direct and indirect food uses of carboxymethyl cellulose and sodium carboxymethyl cellulose.

The Select Committee has reevaluated the available information on carboxymethyl cellulose and its sodium salt. Because carboxymethyl cellulose becomes the sodium salt in the presence of sodium ion, no distinction between the two substances as used in food need be made. There are no data to suggest acute or chronic toxicity of either substance beyond those which are already included in the December, 1973 report on cellulose and cellulose derivatives.

Based upon this reevaluation the Select Committee finds that subsections C and D, pages 18 and 19, of its report, Evaluation of the Health Aspects of Cellulose and Certain Cellulose Derivatives as Food Ingredients, December, 1973, should be clarified to read as follows:

C. CARBOXYMETHYL CELLULOSE

Because carboxymethyl cellulose becomes the sodium salt in the presence of sodium ion, no distinction between the two substances as used in food need be made. Carboxymethyl cellulose is designated GRAS as a substance migrating to food from cotton or cotton fibers used in dry food packaging and is also presumed by FDA to be GRAS but unpublished. In view of all of the foregoing, the Select Committee concludes that:

There is no evidence in the available information on carboxymethyl cellulose that demonstrates or suggests reasonable grounds to suspect a hazard to the public when it is used as a direct or indirect food ingredient at levels that are now current or that might reasonably be expected in future.
D. SODIUM CARBOXYMETHYL CELLULOSE

Sodium carboxymethyl cellulose is designated GRAS as a miscellaneous and/or general purpose food additive. There are no data to suggest that its physiological action differs from that of carboxymethyl cellulose.

In view of the foregoing the Select Committee concludes that:

There is no evidence in the available information on sodium carboxymethyl cellulose that demonstrates or suggests reasonable grounds to suspect a hazard to the public when it is used at levels that are now current or that might reasonably be expected in future.
VI. REFERENCES CITED


15. Asahi Chemical Industry Co., Ltd. 1966. Effect of ingestion of Avicel-contained foods on living organisms. Medical Department, Tokyo University, and Biochemical Department, Toranoman Hospital, Tokyo. (Unpublished report; copy supplied with reference no. 1).


of methylcellulose. Farmakol. Toksikol. 24:342-346. (In
Russian; translation supplied with reference no. 1).


ingestion of methyl cellulose and ethyl cellulose by rats. J. Lab.

26. Bauer, R.O. 1945. Methyl cellulose: its laxative action and
4:112 (abstract).

27. Bargen, J.A. 1949. A method of improving function of the bowel:


dietary feeding studies of Methocel MC in rats. The Dow Chemical
Company, Midland, Mich. 104 pp. (Unpublished report; copy
supplied with reference no. 1).


Holtkamp, and J.W. Newberne. 1968. Teratology and reproduction
studies with an antinauseant. Toxicol. App. Pharmacol. 13:
439-447.

evaluation of FDA 71-51 (Methocel) in mice, rats and hamsters.
Final report prepared under DHEW contract no. FDA 71-260.
Maspeth, N.Y. [44 pp.]


48. The Dow Chemical Company. 1960. [Propylene glycol ether of methylcellulose; Methocel]. Food additives petition no. 72 to Food and Drug Administration. (Unpublished; copy of petition and supporting test data supplied with reference no. 1.).

VII. SCIENTISTS CONTRIBUTING TO THIS REPORT

1. Members of the Select Committee on GRAS Substances:

Aaron M. Altschul, Ph.D., Professor, Department of Community Medicine and International Health, School of Medicine, Georgetown University, Washington, D.C.

Joseph F. Borzelleca, Ph.D., Professor of Pharmacology, Medical College of Virginia, Health Sciences Division, Virginia Commonwealth University, Richmond, Va.

Bert N. La Du, Jr., M.D., Ph.D., Professor and Chairman, Department of Pharmacology, New York University School of Medicine, New York, N.Y.

John R. McCoy, V.M.D., Professor of Comparative Pathology, New Jersey College of Medicine and Dentistry, Rutgers Medical School, New Brunswick, N.J.

Sanford A. Miller, Ph.D., Professor of Nutritional Biochemistry, Massachusetts Institute of Technology, Cambridge, Mass.

Gabriel L. Plaa, Ph.D., Professor and Chairman, Department of Pharmacology, University of Montreal Faculty of Medicine, Montreal, Canada.

Ralph G. H. Siu, Ph.D., Consultant, Washington, D.C.

John L. Wood, Ph.D., Distinguished Service Professor, Department of Biochemistry, University of Tennessee Medical Units, Memphis, Tenn.

George W. Irving, Jr., Ph.D. (Chairman), Research Associate, Life Sciences Research Office, Federation of American Societies for Experimental Biology, Bethesda, Md.

2. LSRO staff:

C. Jelleff Carr, Ph.D., Director, LSRO/FASEB.
Samuel B. Detwiler, Jr., Research Associate, LSRO/FASEB.
Kenneth D. Fisher, Ph.D., Research Associate, LSRO/FASEB.
Andrew F. Freeman, Research Associate, LSRO/FASEB.
3. **Ad hoc** consultant:

Clint P. Nash, Ph.D., Professor of Pharmacology, University of Tennessee Medical Units, Memphis, Tenn.

Report submitted by:

January 21, 1974 (Date)

George W. Irving, Jr., Chairman
Select Committee on GRAS Substances