LIFE SCIENCES RESEARCH OFFICE

THE EVALUATION OF THE SAFETY OF USING PSYLLIUM SEED HUSK AS A FOOD INGREDIENT

December 1993

Prepared for

Kellogg Company
235 Porter Street
P.O. Box 3423
Battle Creek, Michigan 49016-3423

FASEB

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FEDERATION OF AMERICAN SOCIETIES
FOR EXPERIMENTAL BIOLOGY
9650 Rockville Pike
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Prepared by

An ad hoc Expert Panel
of the
Life Sciences Research Office

and edited by

John M. Talbot, M.D.
Sue Ann Anderson, Ph.D., R.D.
Kenneth D. Fisher, Ph.D.

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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 literature reviews and the scientific opinions of knowledgeable investigators engaged in work in specific areas of biology and medicine.

This report is one of a continuing series concerning the health aspects of food ingredients that may be Generally Recognized as Safe (GRAS) food substances. 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 LSRO convened an ad hoc Expert Scientific Panel to conduct an evaluation of the health effects of psyllium seed husk (PSH). This report was prepared for the Kellogg Company, Battle Creek, Michigan, by an ad hoc Expert Scientific Panel and edited by John M. Talbot, M.D., Senior Medical Consultant, LSRO; Sue Ann Anderson, Ph.D., R.D., Senior Staff Scientist; and Kenneth D. Fisher, Ph.D., Director, LSRO, in accordance with a contract between the Kellogg Company and the LSRO, FASEB. Scientists selected as members of the Panel were chosen for their scientific qualifications, experience, and judgment, with due consideration for balance and breadth in appropriate professional disciplines. Members of the Panel and others who assisted in the preparation of this report are listed in Chapter VII.

The Panel and LSRO acknowledge the assistance of Victor Fulgoni, III, Ph.D., of the Kellogg Company and Michael P. Lehmann, Furth, Fahrner & Mason, San Francisco, California, who provided information, data, and background material on PSH. Specifically, the Panel and LSRO thank Dr. Fulgoni and Mr. Lehmann for identifying materials in the several supplements to the Kellogg Company's submissions to the Food and Drug Administration that were pertinent to the Expert Panel's questions during its evaluation.

The Expert Panel met in January and April 1993 to obtain background information, identify and analyze pertinent literature and experimental studies, develop drafts of the report, and reach an opinion as to whether the available information and data on the health effects of PSH are sufficient to meet the regulatory requirements of safety as a GRAS food ingredient. The Expert Panel's evaluation was made independently of the Kellogg Company or of any other governmental or nongovernmental groups. The Expert Panel and LSRO accept responsibility for the study conclusions and the accuracy of the report.

This final report was reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent Society of FASEB) under authority delegated by the Federation Board. Upon completion of these review procedures, the report was approved and transmitted to the Kellogg Company by the Executive Director, FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of each individual member of the constituent Societies.

December 8, 1993
Date

Kenneth D. Fisher, Ph.D.
Director
Life Sciences Research Office

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I. INTRODUCTION

This report addresses the safety aspects of the use of psyllium seed husk (PSH) as a food ingredient in grain-based foods. The report is based on evaluation of information published in the scientific literature as well as data and information provided by the Kellogg Company (Clark, 1992a,b; Clark et al., 1990a,b,c, 1991; Furth et al., 1989a,b,c).

To ensure completeness and currency of the evaluation of safety of PSH, this information has been supplemented by the use of generally available scientific and statistical reference sources and compendia; new, relevant books and reviews and the literature citations contained in them; current literature citations obtained through computer retrieval systems of the National Library of Medicine; relevant data in the files of LSRO; relevant regulatory documents of the Food and Drug Administration (FDA); and the combined knowledge and experience of members of the Expert Panel and the LSRO staff.

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321 (s)] (U.S. Congress, 1993), GRAS substances are exempt from the premarketing clearance that is required for food additives. This Act and the Code of Federal Regulations [21 CFR 170.3 and 170.30] (Office of the Federal Register, 1993a,b) state that GRAS can mean 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 evaluation of results of publicly available credible toxicological testing, which may be corroborated by unpublished studies and data. Further, the Code specifies that expert judgment 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.

The FDA also specifies that persons seeking affirmation of GRAS status of substances must submit a petition for GRAS affirmation that contains all relevant chemical, physical, and biological data related to the intended uses [21 CFR 170.35] (Office of the Federal Register, 1993c). These data must include a description of the physical and chemical properties of the substance, past, current, or intended use in foods, methods for detecting the substance in foods, information that supports safety and functionality, a statement attesting to the balance and representative nature of the submitted information, and a statement affirming that non-clinical laboratory studies were conducted in compliance with Good Manufacturing Practice (GMP) regulations (Office of the Federal Register, 1993d). The petition must also include an environmental assessment or justification for exclusion. Finally, the FDA recognizes [21 CFR 170.30] (Office of the Federal Register, 1993b) that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

The LSRO ad hoc Expert Panel reviewed and evaluated the available information on the safety of PSH in full recognition of the foregoing provisions. In reaching its conclusion of safety, in accordance with FDA's guidelines, the Expert Panel relied primarily on directly related published data as well as on unpublished studies that are in press and other information and data. This report was prepared for use by the Kellogg Company in submitting a GRAS affirmation petition to FDA on PSH under the Federal Food, Drug, and Cosmetic Act. The Expert Panel anticipates that its conclusions would be reviewed if new information on safety of the substance becomes available.

II. BACKGROUND INFORMATION

A. SOURCES OF PSYLLIUM PRODUCTS[1]

Psyllium seed, the seed husk, and the husk gum are derived from several species of herbaceous plants of the genus *Plantago* (BeMiller, 1973). Numerous species of *Plantago* occur worldwide as domesticated and wild plants and weeds. Several species are cultivated in the United States, Mediterranean countries, and India primarily for the seed and seed components.

The product used by the Kellogg Company is blond psyllium, derived from *P. ovata* (Forskal) grown in India (Furth et al., 1989a). *P. ovata* is the species of choice because seed of this species contain a higher percentage of gum (approximately 30 percent) than do seed of other cultivated species, because the blond seed yield a practically colorless mucilage, and because the seed coat of *P. ovata* can be more readily separated from the seed mechanically (BeMiller, 1973).

The psyllium seed husk (PSH) used as a food ingredient by the Kellogg Company is derived from *P. ovata* seed grown in India, imported into the United States by J.B. Laboratories, Inc. (Holland, Michigan), and further refined by J.B. Laboratories and the Kellogg Company prior to use.

B. PROCESSING OF PSYLLIUM SEED

Harvesting and production of PSH and PSH gum are multistep processes. Mature plants are harvested in India from March through April or May (BeMiller, 1973). Plants are pulled or cut and winnowed to separate seeds. The seeds are subsequently sieved to remove chaff and foreign matter. Purified seeds are then ground in a traditional attrition mill which separates the husk from the seed by grinding off the cracked seed husk in a sequential series of emery wheels or the equivalent (Furth et al., 1989a; Van Brunt et al., 1989). The husk fractions are removed in the sequential grinding process, leading to a series of products of successive purity. The first cut is 99 percent pure husk; the second cut, 95 percent pure husk, and so on. PSH is then bagged for transport from India by grade (99 percent, 95 percent, 90 percent, etc).

1. Psyllium seed husk (PSH)

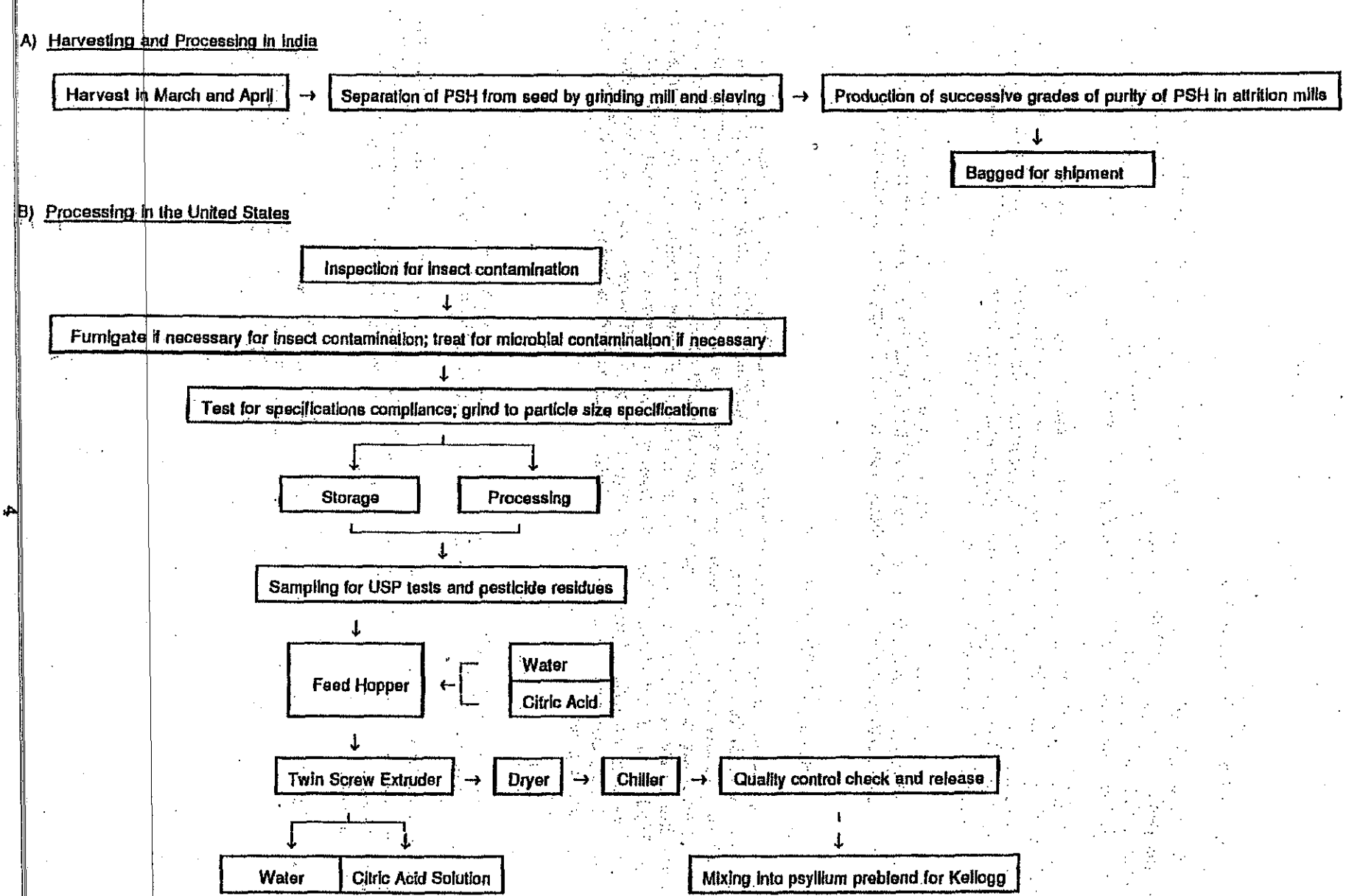
According to information provided by the Kellogg Company (Fulgoni, 1993a), the imported PSH is further processed in the United States as outlined in Figure 1 and as explained below.

Lots are received by J.B. Laboratories, Inc. repalletized and stored in trailers. Trailers are fumigated with methyl bromide and subsequently pallets are removed and stored in a warehouse until used (see Appendix A in Clark et al., 1991). J.B. Laboratories, Inc. also takes lot samples for purity and U.S. Pharmacopeia tests.

Prior to shipping to the Kellogg Company, jute bags of PSH are opened and screened to remove foreign material. Raw PSH at ambient temperature is introduced in dry form through a feed hopper

[1] Definitions of various terms are provided in Appendix A. In this report psyllium is used as a generic term.

FIGURE 1. Harvesting and Processing of Psyllium Seed Husk.



Modified from Fulgoni, 1993a

into the barrel of a twin screw extruder. Ambient water and an ambient homogeneous solution of citric acid and water are injected into the barrel of the twin screw extruder to coat the psyllium husk uniformly. No precipitation or settling out occurs. The pH of the PSH coated with citric acid at this point is approximately 4.8.

The PSH-citric acid mixture is heated in the barrel of the extruder to a temperature of at least 240° F for a period of about 10 seconds. Because of the high pressure in this closed system, the slurry does not reach boiling temperature.

The extruded material is then conveyed through a dryer at 150° F ± 15° F for a period of approximately 30 seconds to 1 minute. The purpose of the dryer is to drive off the excessive moisture in the product.

The conditions of extrusion are as follows (Lehmann, 1993):

Parameter	Limit
Product Temperature	Minimum 240° F
Screw Speed	Target 250 rpm
Product Feed Rate	16 kg/min ± 5%
Water Level in Extruder	15.5-17.5%
Dryer Setting	150° F ± 30° F
Finished Product Moisture	6-10%
Finished Product Temperature	Maximum 100° F

The material is conveyed through a chiller to cool to a temperature of less than 100° F (37° C) to stop the cooking of the material and reduce the possibility for microbial growth. Material exceeding this temperature as it leaves the chiller has been found to result in formation of condensation in the containers which may lead to microbial growth.

The product is milled to the proper particle size and discharged into polyethylene-lined containers. Following a quality control check for microbial contamination and uniformity of particle size, the extruded PSH is mixed in a pre-blend with other grains (e.g., rice flour or oat bran) to Kellogg specifications. The pre-blend is shipped to Kellogg in 1300 lb polyethylene-lined containers (see Appendix A in Clark et al., 1991).

Once received by the Kellogg Company at its Battle Creek Michigan plant, the pre-blend is processed into the ready-to-eat cereals in a closed system. The pre-blend is transferred to a hopper, conveyed to an extruder, and pelletized. Moistened pellets are transported to silos, mixed with basic ingredients, flaked and then toasted in an oven. The resultant cereal flakes are cooled and packed immediately (see Appendix A in Clark et al., 1991).

2. Psyllium seed husk gum

According to the information received from the Kellogg Company (Fulgoni, 1993b), the product for which they seek GRAS status is PSH not PSH gum. However, the gum or mucilage itself is contained within the husk and the gum is typically produced by a separate process. Gum production in India and other countries usually proceeds by extraction of the seed (without the husk removed) with boiling water (BeMiller, 1973). The dispersed gum in water solution is then separated from cellulose and other insoluble materials by gravity (settling), by dilution in water, or frequently in a dilute agar solution. Centrifugation of the dispersed gum solution is an alternate method of gum purification. The diluted solution or centrifuged product is further dried to produce PSH gum.

C. PHYSICAL AND CHEMICAL PROPERTIES

1. Psyllium seed husk

The grade or purity of the PSH depends upon the extent to which the seeds are ground in the attrition mill. The commercial grade PSH used by Kellogg is at least 95 percent pure husk with 5 percent extraneous material, including minute fragments of the seed endosperm and material external to the husk (seed coat).

PSH powder is pale to buff color, with a slight pinkish tinge. PSH can be identified by the presence of large transparent cells that microscopically appear polygonal to slightly rounded (U.S. Pharmacopeial Convention, 1989). When mounted in cresol, PSH is composed of polygonal prismatic cells with 4 to 6 straight or slightly wavy walls. Mounted in ethyl alcohol and irrigated with water, the mucilage in the outer portion of epidermal cells swells rapidly. Microscopic preparations are frequently viewed with ruthenium red/lead acetate in which the mucilage stains red. Cell wall fragments may be present, and the mucilage characteristically stains red when treated with ruthenium red/lead acetate stain (U.S. Pharmacopeial Convention, 1989). PSH and PSH powder are further identified by a standard test for swell volume (U.S. Pharmacopeial Convention, 1989). After 24 hours, the volume of gel for PSH is not less than 35 ml/g for PSH and not less than 40 ml/g for PSH powder. Using the same standard test for psyllium hydrophilic mucilloid (Metamucil®), the gel volume is not less than 110 ml/3.5g = 31.4 ml/g.

According to Kennedy (1979) samples of powdered PSH yielded two fractions when treated with mild alkali (1.2 M NaOH, 5g PSH powder/L alkali): the mucilaginous polysaccharide gum (85 percent) and the non-polysaccharide component (15 percent). The mucilage polysaccharide appears to be a highly branched acidic arabinoxylan. The predominant monosaccharides of PSH gum are D-xylose and L-arabinose. Laidlaw and Percival (1949) extracted psyllium seed with cold water and found the resultant mucilage was 46 percent D-xylose, 40 percent 2-O-L-rhamnose and 7 percent L-arabinose. In subsequent studies using a hot water extraction, Laidlaw and Percival (1950) obtained a mucilaginous solution containing 80 percent D-xylose and 14 percent L-arabinose, but no rhamnose. Using various techniques of extraction, several investigators have determined that the psyllium seed mucilage composition was similar to the above and included D-rhamnose, D-galactose, D-galacturonic acid, 4-0-methyl-D-glucuronic acid, and 2-0 (α-D-galactopyranosyluronic acid)-L-rhamnose as minor constituents (Anderson and Fireman, 1935; Erskine and Jones, 1956; Laidlaw and Percival 1949, 1950; Nelson and Percival, 1942). It should be noted that these early investigations involved extraction of both psyllium seed and PSH. Consequently, it may be presumed that isolated PSH polysaccharide is a highly branched acidic arabinoxylan. The insoluble component of PSH apparently contains no polysaccharide material (Kennedy et al., 1979); it reportedly contains 0.3 percent nitrogen (Van Brunt et al., 1989).

According to information in Appendix E of a letter to LSRO dated February 5, 1993 (Lehmann, 1993), the mucilage of PSH is referred to as an arabanosyl (galactosyluronic acid) rhamnosylxylan. This is consistent with the compositional data cited above. It is of note that the presence of xylose and rhamnose is unique to the polysaccharide derived from psyllium as both are present only in trace amounts in wheat bran, oat bran, and rice hulls.

2. Psyllium seed husk gum

According to BeMiller (1973), purified psyllium seed gum is:

> "a white, fibrous material that hydrates slowly to form viscous dispersions at concentrations up to 1 percent. At 2 percent solids, a clear, gelatinous mass is formed. The dispersions are clear, even though solution is incomplete. Portions of the gum that have hydrated but not dissolved cannot be removed by filtration in the usual manner but can be by centrifugation. When seeds are placed in 25 times their weight of water and left overnight, a dense gel settles out with the seed and the clear solution can be removed by decantation or centrifugation.
>
> Psyllium seed gum dispersions are thixotropic; that is, they show a decrease in viscosity as shear rate is increased, a decrease in viscosity with time at a constant rate of shear, a recovery of viscosity when the shearing stress ceases, and a yield value or force required to produce movement. They are relatively little affected by temperature at temperatures between 20° and 50° [Centigrade] and are unaffected by sodium chloride at concentrations up to 0.15M. There is little change in viscosity with pH in the pH range 2 to 10. No increase in viscosity of *P. ovata* gum dispersions occurs at low pH values because intramolecular hydrogen bonding, which persists up to the point at which ionization of 20 percent of the carboxyl groups is suppressed, prevents expansion of the molecular conformation."

According to BeMiller (1973), the exact composition of purified PSH gum had not been determined. It is presumed to be predominately the acidic highly branched arabinoxylan polysaccharide as the gum constitutes 85 percent of the PSH extractives (Kennedy et al., 1979).

D. FOOD GRADE SPECIFICATIONS AND RESIDUE ANALYSES

1. Psyllium seed husk

Specifications for PSH have been published by the U.S. Pharmacopeial Convention (1989) (Table 1).

In addition, the Kellogg Company has provided more detailed information on the PSH product for which GRAS status is being sought (Table 2) (Fulgoni, 1993a,b). These specifications apply to the material provided by J.B. Laboratories to the Kellogg Company for use in ready-to-eat cereals.

While the Kellogg Company has provided no data on heavy metal and pesticide residues, there are data available in the GRAS petition of General Mills, Inc. (Van Brunt et al., 1989). The General Mills petition references the U.S. Pharmacopeia/National Formulary specifications (1984 edition, similar in content to the 1989 edition). Data in this petition indicate that General Mills, Inc. was using PSH powder in their ready-to-eat cereal, presumably derived from the 85 percent pure PSH imported from India. This assumption is based upon the General Mills, Inc. indication of food grade specifications being those of the U.S. Pharmacopeia. General Mills, Inc. contracted with Twin City Testing Corporation, St. Paul, Minnesota, to measure heavy metal concentrations and silica content in the PSH. Analysis of the PSH powder was conducted between October 4 and 6, 1988. Analytical results indicated the following heavy metal and silica contents of PSH powder:

Table 1. United States Pharmacopeia Specifications for Psyllium Seed Husk.

Total Ash	not more than 4.0 percent
Acid-insoluble Ash	not more than 1.0 percent
Water	not more than 12.0 percent
Swell Volume	not less than 40 ml/g of powdered PSH and not less than 35 ml/g for PSH
Extraneous Matter	light - not more than 15 percent heavy - not more than 1.1 percent
Insect Infestation	for powdered PSH not more than 400 insect fragments per 5.5 grams including mites and psocids for powder; no eggs, larva, or whole insects present; for PSH, not more than 100 insect fragments, including mites and psocids
Microbial Limits	mold and yeast - does not exceed 1000/g (combined); *Salmonella* species - negative; *Escherichia coli* - negative

Table 2. Comparison of United States Pharmacopeia and Kellogg Company Specifications for Psyllium Seed Husk.

Specification	U.S. Pharmacopeial Convention (1989)	Kellogg Company (Fulgoni, 1993a,b)
A. Physical Characteristics		
Form	Powder	Free flowing powder
Color	Pale to medium buff	Pale to medium buff with few dark flakes
Odor	Weak characteristic odor	No off odor. Faint, characteristic odor of psyllium
Flavor	Very mucilaginous taste	No off flavor. Bland mucilaginous taste.
Particle size		U.S.S. Screens on #30 maximum 8.0% on #40 maximum 25% through #100 maximum 25%
Bulk Density (tapped)		0.68 - 0.78 g/ml
Swell volume	Minimum 40 ml/g (for powder PSH), minimum 35 ml/g (for whole PSH)	minimum 55 ml/g
Extraneous matter	Light - Maximum 15% Heavy - Maximum 1.1%	Light - maximum 4.5% Heavy - maximum 0.5% (total not to exceed 4.9%)
B. Composition		
Fat		Maximum 1%
C. Foreign Materials and Contaminants		
Foreign Materials		Free of all substances degrading physical characteristics or deleterious to consumption
Allergenicity		Appropriate assay to ensure removal of protein fractions
Insect Infestation	Maximum 400 insect fragments including mites and psocids for PSH powder; maximum 100 fragments for whole PSH	

Table 2. (Continued).

Specification	U.S. Pharmacopeial Convention (1989)	Kellogg Company (Fulgoni, 1993a,b)
Microbial limits		
Standard aerobic plate count		Maximum 15,000/g
Yeasts	Maximum 1,000/g	Maximum 200/g
Molds	Maximum 1,000/g	Maximum 200/g
Salmonella species	Negative	None detected in 25 g
Escherichia coli	Negative	None detected in 25 g
Staphylococcus aureus		None detected in 25 g
Pseudomonas aeruginosa	Negative	None detected in 25 g

• Arsenic	< 0.2	ppm
• Cadmium	< 0.3	ppm
• Copper	4.4	ppm
• Lead	< 3.0	ppm
• Mercury	< 0.02	ppm
• Silicon (Si)	930	ppm
• Silicon (SiO_2)	2000	ppm

General Mills, Inc. also contracted with Twin City Testing Corporation to measure sulfite concentration in a sample lot of powdered PSH, using the Monier-Williams method; it was < 10 ppm (less than detection limit). General Mills, Inc. screened 2 separate lots of PSH for measurable residues of a select list of 20 pesticides considered to be of greatest potential public health concern, as well as ethylene oxide and methyl bromide. Analyses were performed on October 4 and 20, 1988. Analytical results are noted in Table 3.

The pesticide levels detected (alpha BHC, lindane, DDT), as indicated in Table 3, would be consistent with levels generally found in the commercially available PSH powder, imported from India at that time. These levels are well below the action levels established by the EPA for cereal grain foods (0.05 ppm, 0.01 ppm, 0.5 ppm, respectively). The action levels are established by the EPA in order to limit residues of canceled pesticides to the extent necessary to protect the public health, while taking into account the extent to which the residues in food cannot be avoided by good manufacturing practices. The action levels cited above are published in the 1988 FDA Compliance Policy Guides Manual, Chapter 41, Number 7141.01 (Food and Drug Administration, 1988).

It is well known that these pesticides persist in the environment, and therefore may be present in food crops long after field usage has stopped. The PSH powder previously marketed in a ready-to-eat cereal product by General Mills, Inc. contained no pesticide at a level greater than the EPA-approved tolerance or action level.

2. Psyllium seed husk gum

There are no food grade specifications for PSH gum as it is apparently not used as a food ingredient. (See discussion in next section.)

E. FOOD AND BEVERAGE USES

1. Psyllium seed husk

The GRAS petitions of both the Kellogg Company (Clark, 1992a,b; Clark et al., 1990a,b; Clark et al., 1991; Furth et al., 1989a,b,c) and General Mills, Inc. (Van Brunt et al., 1989) note little use in foods at that time, but cite and document long history of use of psyllium seed, PSH, and presumably PSH gum as foods and beverages. Montague (1932) makes reference to several centuries of use of psyllium seed and mucilage for pharmacological purposes as well as dietary and beverage ingredients. Chopra et al. (1958) and the Indian Council of Medical Research (1987) cite even earlier references (10th century) to use of the mucilage of various *Plantago* species seeds for various dietary and pharmacological properties.

Table 3. Pesticide Residual Levels (ppm) in PSH Powder.

	Lot #1	Lot #2	Detection Limit (ppm)
Alpha BHC	0.013	0.010	0.003
HCB	ND	ND	0.003
Lindane	0.003	0.003	0.003
Heptachlor	ND	ND	0.003
Aldrin	ND	ND	0.003
Heptachlor Epoxide	ND	ND	0.003
Dieldrin	ND	ND	0.003
DDE	ND	ND	0.003
Endrin	ND	ND	0.003
DDD	ND	ND	0.003
p-p' DDT	0.017	0.011	0.003
Methoxychlor	ND	ND	0.003
Mirex	ND	ND	0.003
Diazinon	ND	ND	0.003
Malathion	ND	ND	0.003
Parathion	ND	ND	0.003
Methyl Parathion	ND	ND	0.003
Ethion	ND	ND	0.003
Ethylene Oxide	NT	ND	0.010
Methyl Bromide	NT	ND	0.010

ND = not detected; NT = not tested

In 1982, the Select Committee on GRAS Substances (SCOGS) considered the food uses of several vegetable gums, including PSH gum (Select Committee on GRAS Substances, 1982). The report of the Select Committee indicated that the primary use was as a bulk-type laxative, and it had been used for that purpose since 1930 (BeMiller, 1973; Fingl, 1975). The Select Committee noted that PSH gum was also used in cosmetic products such as hair-setting lotions, in paper and textile manufacturing as a deflocculant, and as an emulsifying agent. Additional uses of the PSH gum cited by SCOGS (Select Committee on GRAS Substances, 1982) included treatment of gastric hypoacidity, in enteric coating materials, or in sustained-release drug preparations, removal of exogenous sodium from the gastrointestinal tract, and inhibition of bacterial growth by its pH effect (BeMiller, 1973).

The Select Committee reported no domestic uses in food. Later, Chan and Wypyszyk (1988) reported that PSH powder had been used experimentally in such products as beverages, a fiber source for bakery products and cookies, cereals, binders in processed and synthetic meats, ice creams, yogurts, sauces, gravies, and soups. They also pointed out that Botanicals International of Long Beach, California, was manufacturing products containing PSH which are used in cake icings and in instant fruit fillings. Chan and Wypyszyk (1988) also stated: "Some pharmaceutical firms have converted medicinal psyllium products into conventional foods like instant beverages, cereals, and candy."

Table 4 summarizes data presented in the Kellogg Company's 5th Supplement (Clark et al., 1991) to its GRAS petition (Furth et al., 1989a) on reported food uses of psyllium seed, PSH, and PSH gum from the early 1900's.

Table 4. Reported Uses of Psyllium in Foods.*

Uses in Foods	Sources
Mixed in water as a cooling drink	American Medical Association, 1927 British Pharmaceutical Codex, 1911
Mixed with fruit extracts	Figg, 1931
Substituted for arrowroot in congee (a type of Asian rice or millet gruel)	Singh and Virmani, 1982
As a spread on bread	American Medical Association, 1927 Figg, 1931; Montague, 1929
Mixed with honey, marmalade, or stewed fruits	Singh and Virmani, 1982 Solis-Cohen and Githens, 1928
Used in soup	Montague, 1929
Mixed with wheat flour as a thickener	Kumar, 1973 Singh and Virmani, 1982
An ingredient in making chocolate	Kumar, 1973 Singh and Virmani, 1982
An ingredient in jellies	Kumar, 1973
In confectionery bases	British Pharmaceutical Codex, 1911 Singh and Virmani, 1982
As a sizing agent or thickener	Kraemer, 1910 Kumar, 1973
As an ice cream stabilizer	Kumar, 1973; Sommer, 1951 Singh and Virmani, 1982 Upadhyay et al., 1978 Anonymous, 1990

* Derived from Clark et al. (1991).

In addition to its recent or current uses in certain Kellogg and General Mills ready-to-eat cereals, psyllium is reportedly sold in bulk as a food ingredient in health food stores in the United States (Van Brunt et al., 1989). In the United States PSH has been consumed as part of a beverage, as a bulk grain, in soup and ice cream, and as a component of cake sizings and fruit fillings. Limited amounts of husk-free psyllium seed are marketed as "health food," but most seed are used as a source of PSH or for animal feed in India (Chan and Wypyszyk, 1988).

2. Psyllium seed husk gum

As noted previously, SCOGS reviewed the uses and safety of PSH gum (Select Committee on GRAS Substances, 1982). Similarly, as cited above, Chan and Wypyszyk (1988) reported various food uses of the medicinal psyllium mucilloid "health food," but most seed are used as a source of PSH or for animal feed in India (Chan and Wypyszyk, 1988).

Based upon a reexamination of the early scientific literature conducted for this study by the Expert Panel and LSRO staff, it appears that the original product of commerce was a mucilage prepared from psyllium seed or PSH by soaking or hot water extraction. More recent investigations have been conducted using PSH powder, the commercially available product for use in medicinals, and more recently in ready-to-eat cereals. Thus, in retrospect, it appears that SCOGS (Select Committee on GRAS Substances, 1982) as well as Chan and Wypyszyk (1988) were referring to extracts of PSH and not the pure PSH gum. For these reasons, it would appear that contemporary uses are based upon a preparation of PSH itself which in reality is 85 or more percent PSH gum.

F. REGULATORY STATUS

Psyllium seed husk was listed as an optional ingredient in the standards of identity for ice cream and other frozen desserts [21 CFR Part 20.1 (f) (2)] (Office of the Federal Register, 1974). In 1975, PSH was listed as an optional ingredient in the standards of identity for frozen sherbets [21 CFR 135.10 (e) (2)] and ice cream [21 CFR 135.30 (f) (2)] and was permitted in ice milk [21 CFR 135.40] (Office of the Federal Register, 1975a,b,c). In 1978, Title 21 of the Code of Federal Regulations no longer listed PSH as an optional ingredient for ice cream, frozen sherbet, or ice milk (Office of the Federal Register, 1978).

SCOGS reported that there were no apparent uses of PSH gum in foods (Select Committee on GRAS Substances, 1982); however, the Select Committee noted that PSH gum had been widely used in this country as a bulk laxative since approximately 1930 and relied upon many of the studies with laxatives to reach a conclusion that PSH gum could be GRAS. The Select Committee was aware of food uses of psyllium seed and PSH gum as animal feed and as food or food ingredients in India and other countries.

In 1986, the FDA, in a review of laxative drug products for over-the-counter human use, published a notice of proposed rulemaking in regard to PSH-containing laxatives (Food and Drug Administration, 1986). The proposed rule recommended doses of over-the-counter laxatives (containing PSH) of up to 30 g/day in divided doses of 2.5 to 7.5 g/dose for adults and children 12 years of age or older, and oral doses of up to 15 g/day in divided doses of 2.5 to 7.5 g/dose for children 6 to 12 years of age. For children under 6 years of age, physician consultation was recommended. The final monograph on over-the-counter laxatives with these proposed rules has yet to be published by the FDA.

At the present time, there are no provisions of the Code of Federal Regulations governing food uses of PSH. The FDA has recently published regulations on warning statements for over-the-counter bulk laxatives containing water soluble gums such as PSH (Food and Drug Administration, 1993a).

G. KELLOGG PRODUCT

The petition for GRAS status of PSH and its supplements, submitted by the Kellogg Company (Clark et al., 1990a,b,c; Clark et al., 1991; Clark et al., 1992a,b; Furth et al., 1989a,b,c) suggest that PSH might be used in 11 of the 43 general food categories listed in 21 CFR 170.3 (n). These include baked goods and baking mixes, beverages, breakfast cereals, confections and frostings, ice creams, pie fillings and puddings, grain products and pastas, gravies and sauces, candy, soups and soup mixes, and meat products (Clark et al., 1990b; Furth et al., 1989a,b,c). However, more recently the Kellogg Company has indicated that it currently contemplates use of PSH in ready-to-eat cereals, breakfast bars, poptarts, bread-based products, and pasta (Fulgoni, 1993b). The General Mills, Inc. petition (Van Brunt et al., 1989) requested GRAS use of PSH in ready-to-eat cereals.

As noted previously, despite the different method of preparing PSH (that is grinding and extrusion versus hot water extraction), the Kellogg petition is for use of PSH. Further, it is evident that scientific information on PSH gum is relevant to the safety evaluation of PSH because this material is in essence at least 85 percent PSH gum. Finally, in this report the term "Psyllium Seed Husk (PSH)" is used to denote the Kellogg product. It appears likely that references to products or studies on psyllium seed extract, psyllium seed mucilloid, psyllium seed gum, and "psyllium" in the early scientific and herbal literature are in fact, references to some type of PSH preparation of unknown purity, somewhat similar to the Kellogg product in chemical composition but variable in regard to physical characteristics.

III. CONSUMER EXPOSURE

Psyllium seed husk has been proposed for use in various grain-based foods by the Kellogg Company. The maximum usage levels of PSH sought for approval by the Kellogg Company are 15 percent by weight in ready-to-eat (R-T-E) cereals, 10 percent in breakfast bars, and 7.5 percent in poptarts, bread-based products, and pasta (Fulgoni, 1993b). The Expert Panel considered bread-based products to include breads and rolls, muffins, doughnuts, biscuits, tortillas, waffles, pancakes, pizza crust, and stuffing. Estimates of the amounts of PSH per serving of foods in these product categories are shown in Table 5. These values were calculated from the maximum levels of use requested by the Kellogg Company and the serving sizes used for the product categories specified in the final rules on food labeling (Food and Drug Administration, 1993b).

For R-T-E cereals, an additional source of information on serving sizes (Anonymous, 1992) was used. This report indicated that persons usually poured "a bowlful, averaging between 1 and 2 cups, no matter how dense or weighty the cereal was." An alternate set of amounts of PSH per serving was calculated for R-T-E cereals based on the R-T-E cereal density categories. These amounts spanned the weight for one cup of cereal at the lower end of the density range to two cups of cereal at the upper end. As shown in Table 5, the amounts of PSH per serving of food, based on the final rules for food labeling (Food and Drug Administration, 1993b), would range from 2.3 g for cereals weighing less than 20 g/cup to 8.3 g for a serving of pancakes. However, if the alternate serving sizes for cereals (Anonymous, 1992) are used, PSH intakes of 12.8 g and 30 g would be expected for persons consuming 2-cup servings of cereals weighing 20 - < 43 g/cup and ≥ 43 g/cup, respectively.

A. USUAL PSYLLIUM SEED HUSK EXPOSURE

In this report the term "usual exposure" refers to mean and selected percentiles of intake of individuals over extended, but indefinite, periods of time (Anderson, 1988). Usual exposure to PSH was estimated by a food consumption model based upon consumption of foods by eaters only in food categories requested for PSH use by the Kellogg Company and the maximum PSH level of addition requested for those foods. The maximum value for PSH concentration in each food category was used to calculate usual exposure estimates to ensure a conservative estimate. Usual consumption of foods was estimated by 3-day consumption of foods commonly eaten by individuals participating in the 1977-78 Nationwide Food Consumption Survey (NFCS) as reported by Pao et al. (1982). In the 1977-78 NFCS, food consumption data were collected for 3 consecutive days during 4 consecutive seasons from 37,874 persons in about 15,000 households (U.S. Department of Agriculture, 1984). Whenever possible, data on 3-day intakes of 200 commonly used foods and food groups included in Pao et al. (1982) were matched as closely as possible with the food categories for PSH use specified by the Kellogg Company. Pao et al. (1982) estimated consumption of R-T-E cereals on the basis of density and sugar content. In this report, two density categories of R-T-E cereals were included because the amount of PSH consumed in R-T-E cereals will be greater in more dense cereals with a constant (15 percent) level of addition. Although pasta was included in the compilations of Pao et al. (1982), dry weight of one serving of pasta was used as the basis for the consumption component because data on the amount of PSH added to pasta were given on a dry-weight basis.

Matches were not possible for some of the products listed by the Kellogg Company. In these cases, the serving sizes designated in the final rules on food labeling (Food and Drug Administration, 1993b) were used as a basis for approximate usual mean intakes of PSH for age/sex groups 4 years of age and older. For 1- to 2-year-old children, serving sizes one-half of those listed were used. Data from Continuing Survey of Food Intakes by Individuals (CSFII) and NFCS 1977-78 suggest that children 1 to 3 years of age consumed about half as much food energy as adult males (U.S. Department of

Table 5. Amounts of Psyllium Seed Husk in Product Categories Specified for Use.

Product Category	Maximum Level of Use[1] % by weight	Serving Size[2] g	Amount per Serving g
Poptarts	7.5	55	4.1
Bread-based products			
Bread and rolls	7.5	50	3.8
Muffins	7.5	55	4.1
Doughnuts	7.5	55	4.1
Biscuits	7.5	55	4.1
Tortillas	7.5	55	4.1
Waffles	7.5	85	6.4
Pancakes	7.5	110	8.3
Pizza crust	7.5	55	4.1
Stuffing	7.5	100	7.5
Pasta	7.5	55[3]	4.1
Breakfast bars	10.0	40	4.0
R-T-E cereals			
< 20 g/cup	15.0	15	2.3
20 - < 43 g/cup	15.0	30	4.5
≥ 43 g/cup	15.0	55	8.3
R-T-E cereals[4]			
< 20 g/cup	15.0	20 - 40	3.0 - 6.0
20 - < 43 g/cup	15.0	20 - 85	3.0 - 12.8
≥ 43 g/cup	15.0	43 - 200	6.5 - 30.0

[1] *Maximum levels of use designated by the Kellogg Company.*

[2] *Serving sizes designated for product categories in the final rules on food labeling (Food and Drug Administration, 1993b).*

[3] *Dry weight for one serving of pasta. Cooked weight of one serving of pasta is 140 g.*

[4] *For ready-to-eat cereals, an additional source of information on serving sizes (Anonymous, 1992) was used. This report indicated that persons usually poured "a bowlful, averaging between one and two cups, no matter how dense or weighty the cereal was." A range of serving sizes was calculated based on the R-T-E cereal categories, spanning the weight for 1 cup of cereal at the lower end of the range to 2 cups of cereal at the upper end.*

Agriculture, 1985, 1986). For estimates of mean usual intake, the serving size listed in the final rules was multiplied by a factor of one-third. These values were considered a reasonable approximation of usual intake because 1) data from the 1977-78 and 1987-88 Nationwide Food Consumption Surveys were used to develop the serving sizes (reference amounts per eating occasion) published in the final rules on food labeling, and 2) it was assumed that these products would be consumed, on average, 1 time during a 3-day period. Intakes of 90th percentile consumers typically have been reported to be 2 to 3 times the mean intake (Food and Drug Administration, 1993b). For estimates of intakes of 90th percentile consumers, it was assumed that twice the mean consumption would be a reasonable approximation of heavy consumers, particularly since the maximum level of PSH addition was used for the estimates. The one-third factor was again applied under the assumption that 90th percentile consumers would also consume these products once during a 3-day period.

Estimates of usual exposure for 11 age/sex groups are shown in Table 6. Values reported are mean and 50th and 90th percentiles for eaters only. In Table 6, the 50th percentile intake was usually considerably lower than the mean intake for each of the age/sex groups, suggesting that a few very high intakes resulted in skewed distributions of intakes. For some age/sex groups, fewer than 50 participants reported consuming a food or constituents of a food group. In these cases, no value was reported for 50th and 90th percentile intakes. Because each value for consumption of items in the various food categories is based on a different group of consumers within the total group of survey participants, values cannot be added across food categories.

Thus, an estimate of total dietary exposure to PSH cannot be calculated from these data. However, inspection of the values in Table 6 indicates that consumption of a product in a single food category would contribute, on average, 0.7 to 2.7 g/day of PSH for consumers in the 1- to 2-year-old age group and 1.3 to 5.7 g/day for 90th percentile consumers in this group. For 15- to 18-year-old males (often the group with the highest food intakes), consumption of a product in a single food category would contribute 1.3 to 5.4 g/day of PSH, on average, and 2.7 to 11.3 g/day for 90th percentile consumers in this group. As a point of reference, the recommended dosage range for PSH taken as Metamucil® is 3.4 to 10.2 g/day (Physicians' Desk Reference, 1992).

B. PSYLLIUM SEED HUSK EXPOSURE PER EATING OCCASION

Estimates of consumer exposure per eating occasion were prepared to provide an indication of the amount of PSH to which consumers might be exposed when consuming a single product containing PSH on a single eating occasion such as a meal or snack. PSH exposure per eating occasion was calculated in an analogous manner to the usual exposure except that quantity consumed per eating occasion was substituted for the estimate of usual intake approximated by 3-day food consumption data. These values are shown in Table 7. Again, the values cannot be added across food categories to arrive at a total intake per eating occasion. These estimates indicate that 1- to 2-year-old children consuming an average-size serving of one food containing PSH per eating occasion would consume 1.9 to 5.3 g of PSH; for the 90th percentile consumers in this age group, intakes from one food per eating occasion would range from 3.8 to 11.0 g of PSH. Adolescent males (15 to 18 years old) consuming an average-sized serving of one food containing PSH per eating occasion would consume 4.0 to 12.1 g, whereas the 90th percentile consumers in this group would have intakes ranging from 7.5 to 21.9 g per eating occasion.

Table 6. Estimates of Usual Psyllium Seed Husk Intakes from Food Categories Specified for Use by the Kellogg Company.

Food category	Maximum level of use in foods (%)[1]	Usual Intake (g/d by Eaters Only) by Selected Age/Sex Groups[2,3]														
		1-2 yr-old ♂ and ♀			3-5 yr-old ♂ and ♀			6-8 yr-old ♂ and ♀			9-14 yr-old ♂			9-14 yr-old ♀		
		mean	50th percentiles	90th	mean	50th percentiles	90th	mean	50th percentiles	90th	mean	50th percentiles	90th	mean	50th percentiles	90th
Poptarts[4]	7.5	0.7	x[5]	1.4	1.4	x	2.8	1.4	x	2.8	1.4	x	2.8	1.4	x	2.8
Bread and rolls[6,7]	7.5	1.1	—[8]	—	1.5	—	—	1.9	—	—	2.2	—	—	1.7	—	—
Muffins and doughnuts[4,9]	7.5	0.7	x	1.4	1.4	x	2.8	1.4	x	2.8	1.4	x	2.8	1.4	x	2.8
Biscuits[6]	7.5	0.5	—	—	0.8	—	—	1.1	1.0	2.0	1.8	1.4	3.0	1.5	1.4	3.0
Tortillas[6]	7.5	1.6	—	—	2.6	1.9	5.7	3.2	1.7	7.5	4.1	3.0	8.8	3.8	2.3	8.3
Waffles[6]	7.5	1.6	—	—	2.3	1.7	5.0	2.2	2.0	4.0	2.7	2.0	5.6	2.4	1.7	5.6
Pancakes[6]	7.5	1.7	1.4	3.7	2.1	1.8	4.1	2.7	2.0	5.5	3.4	2.7	6.8	2.9	2.0	5.4
Pizza[6,10]	7.5	0.7	0.9	2.3	1.1	0.8	2.5	1.3	1.1	2.3	1.8	1.4	3.7	1.6	1.2	3.1
Pasta[4]	7.5	0.7	x	1.4	1.4	x	2.8	1.4	x	2.8	1.4	x	2.8	1.4	x	2.8
Breakfast bars[4]	10.0	0.7	x	1.3	1.9	x	2.7	1.3	x	2.7	1.3	x	2.7	1.3	x	2.7
R-T-E cereal[6] 25-32 g/cup, < 15% sugar	15	1.7	1.2	3.2	2.1	1.5	3.8	2.4	2.0	4.5	2.9	2.6	5.7	2.3	2.0	4.1
50-75 g/cup, all sugar levels	15	2.7	2.6	5.7	3.2	2.6	7.1	3.3	2.6	6.0	4.7	3.8	9.0	3.9	2.6	7.5

See footnotes at the end of Table.

Table 6. (continued).

Food category	Maximum levels of use in foods[1]	Usual Intake (g/d by Eaters Only) by Selected Age/Sex Groups[2, 9]																	
		15-18 yr-old ♂			15-18 yr-old ♀			19-34 yr-old ♂			19-34 yr-old ♀			35-64 yr-old ♂			35-64 yr-old ♀		
		mean	50th percentiles	90th	mean	50th percentiles	90th	mean	50th percentiles	90th	mean	50th percentiles	90th	mean	50th percentiles	90th	mean	50th percentiles	90th
Poptarts[4]	7.5	1.4	x[5]	2.8	1.4	x	2.8	1.4	x	2.8	1.4	x	2.8	1.4	x	2.8	1.4	x	2.8
Bread and rolls[6, 7]	7.5	4.1	—[8]	—	3.0	—	—	4.4	3.9	7.7	2.3	1.8	4.9	3.7	3.4	6.6	2.3	1.7	4.4
Muffins and doughnuts[4, 9]	7.5	1.4	x	2.8	1.4	x	2.8	1.4	x	2.8	1.4	x	2.8	1.4	x	2.8	1.4	x	2.8
Biscuits[6]	7.5	2.2	1.5	5.0	1.5	—	—	2.6	2.5	4.5	1.4	1.0	2.7	2.2	2.0	4.3	1.6	1.0	3.0
Tortillas[6]	7.5	4.7	—	—	3.6	2.9	6.2	6.1	3.5	18.0	4.1	2.3	9.0	5.7	3.5	11.3	3.9	2.3	9.9
Waffles[6]	7.5	3.8	—	—	2.0	—	—	3.6	2.5	7.5	2.6	2.0	5.0	3.2	2.5	6.0	2.2	2.0	4.3
Pancakes[6]	7.5	4.7	3.8	9.2	3.5	2.5	7.3	4.4	3.7	7.3	2.7	2.0	5.4	4.1	2.8	8.1	2.9	2.0	5.5
Pizza[6, 10]	7.5	2.5	2.1	4.9	1.7	1.4	3.7	2.8	2.3	5.1	1.9	1.6	3.4	2.6	2.4	5.4	1.7	1.4	3.3
Pasta[4]	7.5	1.4	x	2.8	1.4	x	2.8	1.4	x	2.8	1.4	x	2.8	1.4	x	2.8	1.4	x	2.8
Breakfast[4] bars	10.0	1.3	x	2.7	1.3	x	2.7	1.3	x	2.7	1.3	x	2.7	1.3	x	2.7	1.3	x	2.7
R-T-E cereal[6] 25-32 g/cup, <15% sugar	15.0	3.5	2.6	7.5	2.2	2.0	4.5	5.9	2.6	5.7	2.0	1.5	3.2	2.7	2.0	5.0	2.0	1.4	3.8
50-75 g/cup, all sugar levels	15.0	5.4	3.8	11.3	3.6	2.6	7.5	4.8	3.8	8.7	3.5	2.6	7.5	4.1	3.0	7.5	3.5	2.6	6.9

See footnotes at the end of Table.

Table 6. (continued).

Footnotes

[1] *The maximum levels of use of psyllium seed husk in foods designated by the Kellogg Company. These values were used for calculations of usual intake.*

[2] *Estimates assume that eaters consumed only products containing psyllium seed husk.*

[3] *Values are not additive across food categories.*

[4] *Estimates based on quantity consumed in 1 serving of product as designated by the Food and Drug Administration (1993b). It was assumed that the average consumer consumed 1 serving of product during a 3-day period and that the 90th percentile consumed twice as much (2 servings) during a 3-day period.*

[5] *An "x" indicates that no estimate was made.*

[6] *Estimates based on quantities consumed by individuals who reported eating these products at least once in 3 days in the USDA 1977-78 Nationwide Food Consumption Survey (Pao et al., 1982).*

[7] *Estimate based on assumption of high fiber, wheat germ, bran, oatmeal, and multigrain breads (Pao et al., 1982).*

[8] *Cell size too small to permit a reliable estimate.*

[9] *Muffins and doughnuts were combined for purposes of this estimate because they were considered as items that were eaten interchangeably.*

[10] *The proportion of crust in pizza was considered to be 40 percent by weight. In the final regulations on food labeling (Food and Drug Administration, 1993b), the weights of one serving of pizza crust and pizza were 55 and 140 g, respectively.*

Table 7. Estimates of Psyllium Seed Husk Intakes Per Eating Occasion from Food Categories Specified for Use by the Kellogg Company.

Food category	Maximum level of use in foods (%)[1]	Intake (g/eating occasion by Eaters Only) by Selected Age/Sex Groups[2,3]															
		1-2 yr-old ♂ and ♀			3-5 yr-old ♂ and ♀			6-8 yr-old ♂ and ♀			9-14 yr-old ♂			9-14 yr-old ♀		
		mean	50th percentiles	90th	mean	50th percentiles	90th	mean	50th percentiles	90th	mean	50th percentiles	90th	mean	50th percentiles	90th
Poptarts[4]	7.5	2.1	x[5]	4.1	4.1	x	8.3	4.1	x	8.3	4.1	x	8.3	4.1	x	8.3
Bread and rolls[6,7]	7.5	2.9	—[5]	—	3.2	3.8	4.3	4.4	4.3	8.6	5.0	4.3	8.6	4.4	4.3	8.6
Muffin and doughnuts[4,9]	7.5	2.1	x	4.1	4.1	x	8.3	4.1	x	8.3	4.1	x	8.3	4.1	x	8.3
Biscuits[6]	7.5	1.9	—	—	2.4	2.3	3.8	2.7	3.0	4.5	4.0	3.0	6.0	3.5	3.0	6.0
Tortillas[6]	7.5	2.0	—	—	2.7	2.3	4.5	4.1	4.3	6.8	5.6	4.5	9.0	5.0	4.5	7.9
Waffles[6]	7.5	4.2	—	—	5.2	3.8	8.5	5.2	3.8	7.5	6.5	5.9	11.3	6.0	4.3	11.9
Pancakes[6]	7.5	4.4	3.8	11.0	5.7	4.1	11.0	7.2	6.1	14.2	8.9	7.5	15.0	7.6	6.1	14.1
Pizza[6,10]	7.5	2.3	2.0	3.8	3.1	2.6	5.4	3.5	3.2	6.5	4.7	3.7	9.2	4.1	3.4	7.3
Pasta[4]	7.5	2.1	x	4.1	4.1	x	8.3	4.1	x	8.3	4.1	x	8.3	4.1	x	8.3
Breakfast bars[4]	10.0	2.0	x	4.0	4.0	x	8.0	4.0	x	8.0	4.0	x	8.0	4.0	x	8.0
R-T-E cereal[8] 25-32 g/cup, < 15% sugar	15.0	2.9	2.3	4.5	3.6	3.8	5.7	4.1	3.8	7.5	5.3	4.5	9.0	4.9	3.8	7.5
50-75 g/cup, all sugar levels	15.0	5.3	4.5	7.5	5.9	5.7	9.0	7.1	7.5	11.3	9.8	7.5	15.0	8.1	7.5	15.0

See footnotes at end of Table.

Table 7. (Continued).

Food category	Concentration in foods (%)[1]	Intake (g/per eating occasion by Eaters Only) by Selected Age/Sex Groups[2,3]																	
		15-18 yr-old ♂			15-18 yr-old ♀			19-34 yr-old ♂			19-34 yr-old ♀			35-64 yr-old ♂			35-64 yr-old ♀		
		mean	50th percentiles	90th	mean	50th percentiles	90th	mean	50th percentiles	90th	mean	50th percentiles	90th	mean	50th percentiles	90th	mean	50th percentiles	90th
Poptarts[4]	7.5	4.1	x[5]	8.3	4.1	x	8.3	4.1	x	8.3	4.1	x	8.3	4.1	x	8.3	4.1	x	8.3
Bread and rolls[5,7]	7.5	5.9	4.3	8.9	4.6	4.3	7.5	4.8	4.3	8.6	4.4	4.3	8.4	4.4	4.3	7.5	3.9	4.3	4.3
Muffins and doughnuts[4,9]	7.5	4.1	x	8.3	4.1	x	8.3	4.1	x	8.3	4.1	x	8.3	4.1	x	8.3	4.1	x	8.3
Biscuits[6]	7.5	4.7	4.5	7.5	3.5	---	---	5.4	4.5	9.0	3.4	3.0	6.0	4.7	4.5	7.5	3.1	3.0	4.5
Tortillas[6]	7.5	7.5	---	---	5.2	4.5	9.0	7.3	7.9	10.7	5.0	4.5	7.9	7.3	6.8	13.5	4.8	4.5	7.9
Waffles[6]	7.5	9.4	---	---	5.9	---	---	8.4	6.0	15.0	7.1	5.9	15.0	8.3	6.4	15.0	5.9	5.9	11.9
Pancakes[6]	7.5	12.1	11.0	21.9	9.1	6.1	16.4	11.9	10.6	21.9	7.4	6.1	13.9	10.1	8.1	16.4	7.7	6.1	16.4
Pizza[6,10]	7.5	6.3	5.5	11.4	4.4	3.7	7.7	7.8	6.6	14.3	5.2	4.6	8.5	7.1	6.8	12.7	4.6	4.1	8.2
Pasta[4]	7.5	4.1	x	8.3	4.1	x	8.3	4.1	x	8.3	4.1	x	8.3	4.1	x	8.3	4.1	x	8.3
Breakfast bar[4]	10.0	4.0	x	8.0	4.0	x	8.0	4.0	x	8.0	4.0	x	8.0	4.0	x	8.0	4.0	x	8.0
R-T-E cereal[8] 25-32 g/cup, < 15% sugar	15.0	6.0	4.5	9.0	4.5	3.8	7.5	5.4	4.5	9.0	4.2	3.8	7.5	4.7	4.2	9.0	3.9	3.8	6.8
50-75 g/cup, all sugar levels	15.0	10.1	7.5	15.0	7.5	7.5	11.3	9.2	7.5	15.0	6.6	7.5	11.3	7.5	7.5	12.5	6.3	6.5	9.0

See footnotes at end of Table.

Table 7. (Continued).

Footnotes

1 *The maximum levels of use of psyllium seed husk in foods designated by the Kellogg Company. These values were used for calculations of exposure per eating occasion.*

2 *Estimates assume that eaters consumed only products containing psyllium seed husk.*

3 *Values are not additive across food categories to estimate total exposure per eating occasion.*

4 *Estimates based on quantity consumed in one serving of product as designated by the Food and Drug Administration (1993b). It was assumed that the average consumer consumed 1 serving of product per eating occasion and that the 90th percentile consumer consumed twice as much.*

5 *An "x" indicates that no estimate was made.*

6 *Estimates based on quantities consumed per eating occasion in the USDA 1977-78 Nationwide Food Consumption Survey (Pao et al., 1982).*

7 *Estimate based on consumption of high fiber, wheat germ, bran, oatmeal, and multigrain breads (Pao et al., 1982).*

8 *Cell size too small to permit a reliable estimate.*

9 *Muffins and doughnuts were combined for purposes of this estimate because they were considered as items that were eaten interchangeably.*

10 *The proportion of crust in pizza was considered to be 40 percent by weight. In the final regulations on food labeling (Food and Drug Administration, 1993b) the weights of one serving of pizza crust and pizza were 55 and 140 g, respectively.*

C. POTENTIAL INTAKE OF CONSUMERS PREFERENTIALLY SELECTING PRODUCTS CONTAINING PSYLLIUM SEED HUSK

Aggregate food consumption data could not be used to calculate total exposure to PSH for mean and 90th percentile consumers; however, the Expert Panel considered an estimate of consumption by heavy consumers necessary for the safety evaluation of PSH. As an alternative to use of the food consumption survey data, a hypothetical set of foods was used to calculate the potential daily intake by consumers who might preferentially select products containing PSH. Such a dietary pattern is possible if consumers select products on the basis of dietary fiber content if PSH is included as a dietary fiber source for nutrition labeling. It was calculated from the maximum level of use of PSH specified by the Kellogg Company and the serving sizes designated in the final rules on food labeling (Food and Drug Administration, 1993b) except for R-T-E cereal for which an 85-g (2-cup) serving of a medium-density cereal was used. (See Table 5.) Food categories included in the calculation were single servings of R-T-E cereal. As shown in Table 8, a consumer selecting foods because they contained PSH could consume nearly 25 g PSH per day.

D. EFFECT OF PSYLLIUM SEED HUSK INTAKE ON TOTAL DIETARY FIBER INTAKE

Estimates of total dietary fiber intake in the United States have been compiled from several sources. Marlett and Bokram (1981) estimated mean fiber intakes for 200 college men and women to be 20 and 13 g/day, respectively. Lanza et al. (1987) estimated mean fiber intakes of 16 and 11 g/day for men and women from a nationally representative sample of the United States population participating in the Second National Health and Nutrition Examination Survey. Anderson et al. (1989) calculated a total dietary fiber content of 5.6 g/1000 kcal (11.2 g for a 2000 kcal diet) for a simulated American diet based on the 1977-78 NFCS household food consumption data. Food consumption data from the 1985 and 1986 Continuing Survey of Food Intakes by Individuals suggest mean intakes of 17.5 and 10.8 g/day of dietary fiber, respectively, for men and women 19 to 50 years-of-age (U.S. Department of Agriculture, 1985, 1986). Children 1 to 5 years-of-age in this survey had a mean intake of 10.2 g/day of total dietary fiber (U.S. Department of Agriculture, 1985). Economopoulos (1993) estimated dietary fiber intakes of 14.5 g/day for men and 10.8 g/day for women from the 1987-88 Nationwide Food Consumption Survey.

Many of the foods in the categories proposed for PSH addition (e.g., poptarts, breakfast bars, and many bread-based products) do not presently represent significant dietary sources of fiber. Incorporation of PSH into these product categories may be viewed as supplying additional fiber sources to the diet. PSH added to cereal products was regarded by the Expert Panel as a possible replacement for other fiber sources. Addition of PSH to products that have not previously contained appreciable amounts of fiber would add 0.7 to 2.7 g of soluble fiber per day, on average, for 1- to 2-year-old children, assuming intake from consumption of only one product category of food containing PSH. (See Table 6.) For the heavy 1- to 2-year-old consumer (90th percentile) soluble fiber intake could increase by 1.3 to 5.7 g, with this same assumption. For adolescent males, the mean increase in soluble fiber intake from consumption of a single product from only one category of food would range from 1.3 to 5.4 g/day and for the heavy consumer in this age range from 2.7 to 11.3 g/day.

Although the data in Table 6 should not be added to estimate total exposure because of differences in groups of consumers for each food category, an estimate of PSH intake was made for consumption of multiple products containing PSH. These food categories (R-T-E cereal, poptart, pizza, and bread) were chosen because they probably would not be substituted for one another by consumers, and they might reasonably be expected to be consumed on a regular basis. It is recognized that this approach may overestimate consumption of PSH from these food categories, but it should not overestimate PSH intake from the number of foods in which PSH is proposed for use. Consumption of the average

Table 8. Potential Daily Intake of Psyllium Seed Husk for a Hypothetical Consumer Preferentially Selecting Products Containing Psyllium Seed Husk.

Food Category[1]	Amount Consumed g	Maximum Level of Use[2] % by weight	Psyllium Seed Husk Intake g/day
R-T-E cereal	85[3]	15.0	12.8
Poptart	55[4]	7.5	4.1
Pizza	140[4,5]	7.5	4.1
Bread	55[4]	7.5	3.8
Total			24.8

[1] *Selected from food categories designated for psyllium seed husk addition by the Kellogg Company.*

[2] *The maximum level of use designated by the Kellogg Company was used for calculations of psyllium seed husk intake.*

[3] *This value is the maximum weight of 2 cups of cereal in the weight category 20 - < 43 g/cup.*

[4] *Serving sizes designated for product categories in the final rules on food labeling (Food and Drug Administration, 1993b).*

[5] *Estimate assumes that 40 percent of pizza weight (55 g per serving) is contributed by crust.*

amounts of products containing PSH in these types of products could reasonably be expected to result in usual PSH (additional soluble fiber) intakes as high as 5.2 g/day for average consumers in the 1- to 2-year-old group and 13.4 g/day for average male consumers 15 to 18 years of age.

In general, it has been reported that about two-thirds of total dietary fiber in the North American diet is insoluble fiber with the remaining one-third soluble fiber (Stephen, 1990) which suggests that mean soluble fiber intakes might typically range from about 4 to 7 g/day for adults in the United States. Additional soluble fiber intakes from PSH might reasonably be expected to double or triple the average usual intake of soluble fiber, resulting in soluble fiber making a greater contribution to total dietary fiber intake of the United States population than it has in the past.

IV. BIOLOGICAL EFFECTS

A. DIGESTION, ABSORPTION, METABOLIC EFFECTS, FERMENTATION, EXCRETION

1. Digestion and absorption

Little is known about the digestion and absorption of psyllium by humans. Although most studies suggest that various forms of psyllium are not absorbed from the small intestine, Andersen et al. (1988) found that 1-6 percent of PSH was hydrolyzed in the stomachs of healthy male volunteers, with formation of free arabinose. Intestinal absorption of the free arabinose was 85-93 percent. These investigators concluded that PSH is hydrolyzed solely in the stomach in human subjects and that no further decomposition occurs in the small bowel. Studies of fermentation of PSH in human subjects are reviewed in Section A. 3b, below.

2. Metabolic effects

The principal reported metabolic effects of PSH concern carbohydrate and lipid metabolism. Table 9 lists examples of studies that have demonstrated postprandial reductions in serum glucose and insulin responses as a result of psyllium administration. Other studies have examined whether psyllium preparations influence serum lipid levels and/or serum levels of minerals, vitamins, and other components (Abraham and Mehta, 1988; Anderson et al., 1988; Bell et al., 1988; Burton and Manninen, 1982; Danielsson et al., 1979; Enzi et al., 1980; Fagerberg, 1982; Frati-Munari et al., 1983; Kies, 1983; Liberthal and Martens, 1975).

In 7 of 10 studies which involved consumption of supplements of PSH or psyllium hydrophilic mucilloid by healthy adult volunteers or patients with NIDDM or unclassified diabetes, etc., postprandial glucose and insulin levels were significantly reduced. Two studies on the effects of psyllium in hypercholesterolemic subjects revealed no effect on serum glucose levels, as did one study in healthy volunteers.

Table 10 lists examples of studies of the effects of psyllium on serum lipids. In general, these double-blind, placebo-controlled human studies have shown a total cholesterol lowering of 4 to 6 percent compared with controls and include a reduction of LDL-cholesterol of 5 to 9 percent (Schaller, 1990). Carlson (1987) reported that psyllium in bulk laxatives caused reduction in total cholesterol of 10-15 percent.

a. Effects on biliary function

Beher and Casazza (1971) added 0 or 4 percent Metamucil®, (about 50 percent psyllium seed hydrocolloid (20 g psyllium seed hydrocolloid/kg diet) or about 0.9 g/kg body weight/day) to stock diets containing 5 percent fiber of an unspecified source. These diets were fed to groups of eight rats for 3 weeks before intraperitoneal injection of [^{14}C]cholic acid or [^{14}C]chenodeoxycholic acid. Addition of psyllium seed hydrocolloid increased the turnover rate of both deoxycholic and chenodeoxycholic acids and increased the size of the chenodeoxycholic acid pool. Groups of 18 hamsters fed a gallstone-inducing diet with the addition of 5 percent psyllium seed hydrocolloid (approximately 4.2 g/kg/day) developed no gallstones, whereas 7 of 12 surviving hamsters whose diets were not supplemented with psyllium seed hydrocolloid had gallstones at the end of 1 month (Bergman and van der Linden, 1975).

Table 9. Effects of Psyllium on Postprandial Glycemia and Insulin Responses.*

SOURCE	TYPE OF STUDY	SUBJECTS	SUBSTANCE TESTED	DOSE AND ROUTE	DURATION	BASAL DIET	RESULTS AND COMMENTS
Pastors et al., 1991	placebo-controlled crossover trial	18 noninsulin-dependent diabetics	psyllium hydrophilic mucilloid (Metamucil®)	2 doses of psyllium mixed in H_2O per crossover period, one before breakfast, one before dinner	~15 h for each of 2 crossover periods	regulated NIDDM diets; 12 pts took oral hypoglycemic drugs	postprandial glucose level ↓ 14% after breakfast; 20% after dinner; 31% after lunch; insulin level ↓ 12% after breakfast
Vuksan et al., 1990a	acute test meal bio effects	healthy volunteers; number not stated	PSH (in psyllium-enriched cereal)	4 to 16 g/d PSH in cereal	not stated	not stated	progressive, dose-related decline in blood glucose response
Vuksan et al., 1990b	dietary test of psyllium and glycemic index	10 normal 6 diabetic subjects	PSH (in psyllium-enriched cereal)	10 g PSH	not stated	not stated	markedly reduced glycemic responses in normal and diabetic subjects, authors say reduced rate of digestion is key factor
Bell et al., 1989	DB, PC, parallel	75 hypercholesterolemic pts (38♂, 37♀)	psyllium hydrophilic mucilloid	3.4 g PSH, t.i.d., a.c., oral	8 wk	Step 1 diet (≤ 300 mg Chol, 30 en% F, 55% CHO, 15% P	no effect on serum glucose levels; this was a cholesterol study (see Table 10).
Watters and Blaisdell, 1989	subchronic, placebo-controlled dietary test	db/db diabetic mice	"soluble psyllium fiber"	2.5% of defined mouse diet	18 wk	Guildford Mouse Breeder Chow 911	fasting serum glucose reduced; insulin levels elevated
Anderson et al., 1988	DB, PC, parallel	26 hypercholesterolemic ♂	psyllium hydrophilic mucilloid	3.4 g PSH, t.i.d., a.c., oral	8 wk	usual diet (<300 mg Chol, 20 en% P, 40% CHO, 40% F)	no effect on serum glucose levels; this was a cholesterol study (see Table 10).
Abraham and Mehta, 1985	dietary trial	9 healthy adult men	PSH	21 g/d incorporated into food	21 d	controlled diets, en = 20% P, 35% F, 45% CHO	mean plasma values for G, I, and glucagon after 2 meal tolerance tests were within normal ranges

* See code for abbreviations at end of table.

Table 9. (continued).

SOURCE	TYPE OF STUDY	SUBJECTS	SUBSTANCE TESTED	DOSE AND ROUTE	DURATION	BASAL DIET	RESULTS AND COMMENTS
Frati-Munari, et al., 1985	GTT with PSH	8 healthy adult men	PSH	GTT, G mixed with 10 g PSH GTT, 10 g PSH 30 min before G	~15 h including 12-h fast	fasting	GTT, G and PSH together = ↓ peak serum G and I; no effect when PSH given 30 min before G
Frati-Munari, et al., 1983	clinical trial	9 adult pts with NIDDM 19 overweight adults	psyllium hydrophilic mucilloid	15 g t.i.d., a.c.	10 d	"usual diet"	fasting blood glucose in NIDDM pts ↓ (mean = 27.6 mg/dl); in overweight subjects (mean = 5.6 mg/dl); NIDDM pts also received hypoglycemic drugs
Fagerberg, 1982	open controlled clinical trial	37 adult outpatients with NIDDM	psyllium hydrophilic mucilloid	3.6 - 7.2 g/d of PSH for 2 mo; 10.8 g/d for 2 more mo	4 mo	"regulated" diet	long acting ↓ in fasting blood glucose levels; pts also received hypoglycemic drugs
Capani, et al., 1980	clinical trial	9 hosp diabetic pts	purified extract of psyllium seed	7 g psyllium "product" t.i.d., a.c., oral	9 d	1800 - 2000 kcal/d	progressive ↓ in blood glucose levels after 3 d of treatment; pts also received insulin or a hypoglycemic drug

CODE FOR ABBREVIATIONS IN TABLE 9

a.c.	=	before meals	hosp	=	hospitalized
CHO	=	carbohydrate	I	=	insulin
Chol	=	cholesterol	NIDDM	=	non-insulin dependent diabetes mellitus
DB	=	double-blind	P	=	protein
en	=	energy	PC	=	placebo controlled
F	=	fat	PSH	=	psyllium seed husk
G	=	glucose	pts	=	patients
GTT	=	glucose tolerance test	t.i.d.	=	three times a day

Table 10. Effects of Psyllium on Serum Lipids.*

SOURCE	TYPE OF STUDY	SUBJECTS	SUBSTANCE TESTED	DOSE AND ROUTE	DURATION	BASAL DIET	RESULTS AND COMMENTS
Jenkins et al., 1993	randomized, crossover, non-blinded dietary trial	43 healthy adults (28♀, 15♂) with history of mild to severe hyperlipidemia	2 metabolically controlled low-fat, low-cholesterol diets high in soluble fiber (⅓ soluble, ⅔ insoluble) or insoluble fiber (1/8 soluble, 7/8 insoluble). Diet high in soluble fiber included a psyllium-containing cereal	ad libitum consumption of the test diets	2 four-mo dietary periods separated by 2 mo on a NCEP Step 2 diet	NCEP Step 2 diet	with the soluble fiber diet, mean changes were: total Chol, LDL, and HDL ↓ 4.9 ± 0.9, 4.8 ± 1.3, and 3.4 ± 1.3 percent respectively, compared with concentrations in the insoluble fiber diets; no significant change in total chol: HDL between the 2 diet periods; and loss of bile acids 83 ± 14 percent greater with soluble fiber. Authors concluded soluble fiber lowers blood chol even when intake of dietary fat and chol is markedly restricted
Stoy et al., 1993	randomized, DB, dietary intake of RTE cereals and NCEP diet	24 hypercholesterolemic male volunteers	PSH vs wheat bran	RTE cereal with 15 g soluble fiber and 22.2 g total fiber/d	4 wk baseline, then double crossover 8, 5, 5 weeks	NCEP diet plus 2 oz RTE cereal in am, 1 oz in pm	in baseline periods 8% ↓ in Chol and LDL, no change in PT or HDL or PSH; 4.3% ↓ in Chol and 6.1% ↓ in LDL over 18 wk on PSH
Anderson et al., 1992	randomized, DB dietary test	44 hypercholesterolemic ambulatory pts	PSH-enriched RTE cereal	5.15 g psyllium/d	7 wk	American Heart Association Step 1 diet	serum Chol and LDL ↓ compared with controls; HDL and PT unchanged
Bell et al., 1989	randomized, DB, PC parallel study	75 pts with mild to moderate hypercholesterolemia	psyllium hydrophilic mucilloid	10.2 g/d	8 wk	American Heart Association Step 1 diet for 12 wk before PSH treatment	4.8% ↓ in Chol; 8.2% ↓ in LDL-Chol; 8.8% ↓ in apolipoprotein B

* See code for abbreviations at end of table.

Table 10. (continued).

SOURCE	TYPE OF STUDY	SUBJECTS	SUBSTANCE TESTED	DOSE AND ROUTE	DURATION	BASAL DIET	RESULTS AND COMMENTS
Taneja et al., 1989	dietary test of PSH, lipid absorption and excretion	11 healthy adolescent girls	PSH	25 g/d, oral	two 3-wk periods	first period: a low-fiber diet; second period: diet supplemented with PSH	in second period fecal excretion of total F ↑; serum levels of total lipids, Chol, PT, free fatty acids and phospholipids ↓
Abraham and Mehta, 1988	dietary test of metabolic effects of a psyllium supplement	7 adult male volunteers	ground PSH	21 g/d	3 wk	controlled diet	after 10 d and 3 wk total Chol, LDL-Chol and HDL-Chol ↓; PT, retinylesters, glucose, insulin, and glucagon unchanged at end of test period
Anderson et al., 1988	DB, PC dietary trial	28 hypercholesterolemic men	PSH	3.4 g t.i.d., a.c., oral	8 wk	usual diets (<300 mg Chol/d)	Chol ↓ from 247 to 211 mg/dl in PSH supplemented group; but only 8 mg/dl in placebo group
Carlson (Rydelle Laboratories), 1987	DB, crossover study of PSH and serum C	36 healthy adults (29♀, 7♂), regular users of a bulk laxative	PSH	10.2 g/d oral	6 wk	usual American diet	mean serum Chol = 213 mg/dl compared with 241 mg/dl at start of study
Abraham and Mehta, 1985	dietary trial	9 healthy adult men	PSH	21 g/d incorporated into food	21 d	controlled diets, en = 20% P, 35% F, 45% CHO	fasting plasma Chol ↓ >10% in 7 of 9 subjects
Borgia et al., 1983	clinical test of PSH bulk-forming laxative	65 adult pts with chronic constipation	PSH	3.5 g t.i.d., oral	4 wk	usual diets	no significant changes in serum Chol, PT, and HDL-Chol compared with pretreatment values

* See code for abbreviations at end of table.

Table 10. (continued).

SOURCE	TYPE OF STUDY	SUBJECTS	SUBSTANCE TESTED	DOSE AND ROUTE	DURATION	BASAL DIET	RESULTS AND COMMENTS
Fagerberg, 1982	open, controlled dietary test	40 constipated diabetic patients	psyllium hydrophilic colloid	20 pts = 3.6 g/d 20 pts = 7.2 g/d all pts = 10.8 g/d	60 d 60 d 60 more d	"regulated diet"	Chol ↓ PT and HDL-Chol unchanged; pts were on regulated diets and oral hypoglycemic agents
Enzi et al., 1980	crossover study of effect of psyllium on body wt and serum lipids	28 healthy but obese women	psyllium hydrophilic mucilage	6 g/d in H_2O before meals	30 d per crossover period	800 kcal hypoglucidic diet	plasma Chol and PT ↓; body wt ↓
Danielsson et al., 1979	self-controlled dietary intervention	10 healthy volunteers	psyllium hydrophilic colloid	7.2-10.8 g/d	4 wk	normal diets	no reduction in Chol or PT
		13 pts with essential hyperlipoproteinemia	psyllium hydrophilic colloid	7.2-10.8 g/d	2-29 mo (average: 8 mo)	normal or specific lipid lowering diets	16.9% ↓ in Chol and 52% ↓ in PT
Lieberthal and Martens, 1975	dietary test of PSH and serum Chol	10 hosp pts with serum Chol >280 mg/dl; 9 pts with normal serum Chol	PSH	3.85 g t.i.d., oral	5 wk	usual diets	serum Chol ↓ in 8 of 10 hypercholesterolemic pts and in 6 of 9 pts whose initial Chol levels were in normal range
Garvin et al., 1965	dietary test of PSH and serum Chol	15 healthy adult men	PSH	3.2 g t.i.d. with meals	5 wk	self-selected normal diets	mean serum Chol ↓ 9% below levels in control period; ↓ 7% for subjects on egg-supplemented diet (4-6 eggs/d)

CODE FOR ABBREVIATIONS IN TABLE 10

Chol	=	cholesterol	HDL (HDL-Chol)	=	high density lipoprotein-Chol
DB	=	double-blind	LDL (LDL-Chol)	=	low density lipoprotein-Chol
dl	=	deciliter	NCEP	=	National Cholesterol Education Program
en	=	energy	PC	=	placebo controlled
F	=	fat	PT	=	plasma triglycerides
hosp	=	hospitalized	pts	=	patients
			RTE	=	ready-to-eat

The concentration of deoxycholic acid and the ratios of cholic:chenodeoxycholic acid and cholic:deoxycholic acid were increased in hamsters fed the diet supplemented with psyllium seed hydrocolloid.

Watters and Blaisdell (1989) fed dB/dB diabetic mice soluble psyllium fiber at 2.5 percent of a defined mouse diet for 18 weeks and observed a reduction in serum glucose levels but an increase in insulin levels.

3. Fermentation

Thirteen studies on the fermentability of PSH were selected for review. These studies can be divided into three general categories: (1) animal studies; (2) human studies; and (3) in vitro studies with human or animal microflora.

a. Animal studies

Leng-Peschlow (1991) reported higher levels of total acetate in cecal contents and feces of rats fed supplements of psyllium seeds or PSH compared with rats fed wheat bran. Fecal bacterial mass was increased by psyllium seed and PSH to a greater degree than with wheat bran supplementation. Edwards et al. (1992) reported up to 50 percent fermentation of psyllium in the intestines of rats fed 0.5, 1.5, or 5 percent psyllium added to the basal diet. The basal diet contained about 4.5 percent fiber from nonpurified sources (corn flour).

African green monkeys fed supplements of PSH or cellulose and two levels of cholesterol for 3.5 years showed fiber-related differences in colonic microbial metabolism (Costa et al., 1989a). Compared with cellulose, PSH feeding decreased percentage of dry matter, beta-glucuronidase activity, and pH and increased ammonia nitrogen and short-chain fatty acids (SCFA) output in feces and colon contents. The ratio of anaerobic to aerobic bacteria was lower in colons of PSH-fed animals. The authors suggested that chronic intake of PSH resulted in greater colonic microbial metabolism compared with cellulose intake.

In summary, two in vivo studies in rats and one long-term study in monkeys revealed substantial degrees of psyllium fermentation based on increased colonic production of SCFA.

b. Human studies

Four human subjects on strictly controlled diets were given a fiber supplement, 25 g/day of ispaghula husk (Isogel-PSH) for two 5-day experimental periods (Prynne and Southgate, 1979). Three subjects showed considerable increase in fecal bulk; very little change occurred in one subject. During the 5-day experimental periods in which complete metabolic balance studies were conducted, apparent digestibility of the supplement was generally high; one subject appeared to ferment the Isogel completely. Only one subject showed distinct decreases in the apparent digestibility of energy, nitrogen, and fat in the diet.

In a double-blind crossover study with 7 healthy human volunteers receiving supplemental PSH (ispaghula) 9 g three times daily during two 12-day periods, Marteau et al. (1990) reported that ispaghula was poorly fermented and did not promote gas formation.

In a study of the effect of different modes of administration of PSH on glycemic response and carbohydrate digestibility in normal human subjects, Wolever et al. (1991) found that mixing PSH with or incorporating it into a flaked bran test meal reduced the rate of digestion of the bran flakes in vitro. There was no increase in breath hydrogen levels in vivo (an index of rapid colonic

fermentation). However, the lack of an increase of breath hydrogen does not indicate a lack of microbial degradation of PSH.

Wolever and Robb (1992) studied the effects of 15 g PSH and four other purified fibers on breath hydrogen and methane over a 12-hour period in 8 healthy subjects. None of the fibers had a significant effect compared with fasting in control subjects. Eight healthy subjects consuming a polysaccharide-free diet were fed supplements of guar or PSH in random order over a 3-day study period (Wolever et al., 1992). Twenty grams of guar or PSH taken at breakfast had no effect on breath hydrogen levels over 14 hours. Guar, but not PSH, increased breath methane and serum acetate concentrations.

One of the five studies reviewed here revealed a high apparent digestibility (fermentability) of PSH supplements. The remaining four studies showed no evidence of psyllium fermentability in the human bowel, based on breath hydrogen and methane and serum acetate. However, the absence of an increase in breath hydrogen does not necessarily indicate a lack of microbial degradation of PSH.

In summary, the results of the in vivo studies described above suggest that, although some breakdown of PSH occurs in the intestine, the available data are insufficient to quantify the overall extent of PSH fermentation in the human colon.

c. In vitro studies

Costa et al. (1989b) compared the effects of PSH or cellulose on the metabolism of colonic microflora from African green monkeys using a continuous culture system. The monkeys had been fed supplements of PSH or cellulose for more than 3 years. Cultures from PSH-fed animals had lower pH and higher SCFA concentrations and β-glucuronidase activity than cultures from cellulose-fed animals. The ratio of anaerobes to aerobes was lower in the cultures from the PSH-fed animals. The lower pH and higher SCFA concentrations in the cultures from PSH-fed animals compared with those from cellulose-fed animals suggests that, in this model, PSH is more fermentable than cellulose.

Psyllium is fermented in vitro by bacteria of the human fecal and intestinal microflora (Clausen et al., 1991; Gibson et al., 1990; Horvath et al., 1983; McBurney and Thompson, 1989; Salyers et al., 1978; Tomlin et al., 1989). In contrast to the findings of McBurney and Thompson (1989), compared with other polysaccharides, the in vitro fermentability of PSH by human fecal bacteria is slow (Gibson et al., 1990; Horvath et al., 1983). Tomlin et al. (1989) reported that, while in vitro fermentation of PSH produced significant amounts of hydrogen and methane, these amounts were much lower than those generated by 6 other polysaccharides. Haynes and Lupton (1989) investigated the effect of supplements of psyllium and cellulose on food intake, fiber fermentability, pH, and types and amounts of SCFA produced in healthy women. For the SCFA, the test fibers were anaerobically fermented using fecal inocula. SCFA production from psyllium was 1.8 times greater than with cellulose, and post-fermentation pH values were lower with psyllium, which corresponded to a decreased recovery of psyllium as compared with cellulose.

Jenkins et al. (1993) tested the fermentative ability of human colonic bacteria obtained from subjects who had consumed high-fiber diets for periods of 4 months. The substrates for these tests were wheat bran, PSH, lactulose, and amylose starch. Consumption of high-fiber diets was associated with increased in vitro methane production and reduced hydrogen production. PSH was unusual in producing a significant amount of SCFA with minimal hydrogen and overall gas production. The recovery of PSH was greater than with wheat bran.

In summary, psyllium is fermented in vitro by bacteria of the human fecal and intestinal microflora, and in vitro fermentation of psyllium exceeds that of cellulose except for one study in which recovery of psyllium was greater than with wheat bran.

4. Excretion

In the intestine, psyllium becomes an integral part of the fecal mass (Atal and Kapur, 1963). According to BeMiller (1973), when taken with an adequate amount of water, psyllium "...not only swells and increases the size of the fecal mass, but its mucilaginous dispersions have a lubricant effect...." Prynne and Southgate (1979) reported that 3 of 4 human subjects who consumed 25 g/day of PSH for 3 weeks showed a considerable increase in fecal bulk, and total fecal weight was more than doubled in 2 of the 4 subjects. The ability of PSH to increase fecal bulk has been described by numerous authorities on gastrointestinal physiology. For example, Jenkins (1990) noted: "...psyllium appears to be fermented slowly in the colon and the slow rate of fermentation may account for its ability to increase fecal bulk." As noted by Friedman, (1975): "...hydrophilic colloids derived principally from the indigestible husk of the psyllium seed are the natural vegetable substances which provide to the intestinal contents the non-absorbable and water-retaining bulk that diet does not."

Cummings (1993) listed the results of selected human studies of the effects of gums and mucilages, including PSH/ispaghula, on fecal output. The average increase in fecal output was 3.7 g (±0.5 g SEM) per g of fiber fed. For wheat fiber the increase was 5.4 g (±0.7 g SEM) and for cellulose it was 3.5 g (±0.8 g SEM).

Stevens et al. (1988) compared the effects of dietary supplements of wheat bran, PSH, wheat bran and PSH combined, and a low-fiber diet on transit time and stool characteristics in 12 female subjects over a period of 2 weeks. Fiber supplements decreased transit time, increased the number of daily bowel movements, and increased the wet and dry weights of stools. PSH affected transit time less than bran but increased the amount of water in stools, and the total stool weight more than bran.

B. EVALUATION FOR TOXICITY

1. Animal studies

Fraschini (1978) conducted acute toxicity and other toxicological studies with 3 commercial formulations of purified PSH (Metamucil®). The formulations, in aqueous suspension, were administered by gavage to groups of 5 male and 5 female Swiss mice (20-23 g body weight) or Sprague-Dawley rats (120-140 g) in doses of 1.5, 3.0, and 6 g/kg body weight. No deaths occurred within the 7-day observation period. Slight sedation during the first few hours was observed in animals after administration of the highest dosage. Diarrhea occurred in mice given 6 g/kg body weight of the formulation that contained 49.7 percent glucose.

MacKay et al. (1932) reported a gray-black color in the kidneys of rats (number not stated) and 2 young dogs fed diets containing 25 percent finely ground psyllium seed for 125 and 30 days, respectively. The epithelial cells of the kidney tubules of the rats contained fine brown granules, but those of the dogs showed no similar changes. Various tests failed to identify the chemical nature of the pigment, and the authors reached no conclusions about possible mechanisms. Rats and cats fed diets containing 4 and 19 percent, respectively, of powdered psyllium seed exhibited marked dark pigmentation of the kidneys. Urea clearance was not diminished in the psyllium-fed rats (Thienes and Hall, 1941).

Coulston and Seed (1956) fed rats various fractions of *P. ovata* and *P. arenaria* at 10 percent of the basal diet for 28 weeks to examine possible renal effects. The kidneys of rats fed tailings (PSH treated to remove mucilage fractions) of PSH were brown, but no microscopic pigment was observed. Weight gain and behavior were normal in all test groups.

In rats, 10 percent psyllium seed powder in the diet exerted a protective effect against toxic doses of sodium cyclamate; 2.5 or 5 percent in the diet protected rats against toxic effects of Tween 60 (polyoxyethlene sorbitan monostearate) (Ershoff and Marshall, 1975).

Groups of 3 male and 3 female beagles, 10-12 months old, were fed 250 or 750 mg/kg/day of purified PSH for 6 months (Mercatelli et al., 1979a,b,c). There were no statistically significant differences in body weight gains or food consumption between the treated and control groups at 1, 3, or 6 months. No changes related to treatment were observed at these time intervals in hematological or urinary parameters, or in hepatic function. At 6 months, statistically significant dose-dependent changes ($P < 0.05$) in the blood chemistry of males were lower levels of total protein, total cholesterol, and glucose, and higher levels of nonesterified fatty acids. Total cholesterol and glucose levels in females receiving the higher treatment level were significantly lower than those in controls. Inorganic phosphorus concentrations were significantly greater in both females and males given 250 mg/kg/day of PSH, and both sodium and potassium ion levels were higher in females given 750 mg/kg/day. No significant differences between the mean organ weights of the treated and control groups were found on necropsy at 6 months. Histopathological examination of 31 organs and other tissues showed no changes attributed to treatment (Mercatelli et al., 1979a,b,c).

Psyllium seed husk (800 mg/kg body weight/day) was fed to 2 groups of 4 male and 4 female beagles, 10-12 months old, in their regular diet (Salerno et al., 1978). The PSH was fed to each group for 15 days of the 30-day study in a crossover design. The study was repeated with the same animals fed diets containing 5 percent cholesterol and 20 percent pork fat. Transient decreases ($P < 0.05$) in plasma-free and total cholesterol in animals given PSH gum were noted in both trials. No changes were reported in food consumption, growth, or general behavior or in blood biochemistry values (glucose, nonesterified fatty acids, plasma albumin, and plasma globulin components).

Fraschini (1978) administered daily doses of 2 formulations of PSH (49 and 56 percent psyllium) to groups of 10 male and 10 female Sprague-Dawley rats (120 g average body wt), 6 days each week, for 25 weeks. The 49 percent formulation, in aqueous suspension, was given by gavage in doses of 0.5 and 1.0 g/kg body weight; the 56 percent formulation was administered similarly at the higher dosage. No statistically significant differences were observed between the treated and control groups in results of hematological, hematochemical, and urine tests, in mean body weights, or in organ:body weight ratios of the heart, liver, spleen, kidneys, adrenals, and testes. The investigators reported that no changes attributable to treatment were observed on microscopic examination of the heart, lungs, liver, spleen, kidneys, adrenals, testes, ovaries, or gastrointestinal tract.

Fraschini (1978) also administered the 49 percent psyllium formulation to groups of 2 male and 2 female adult beagles in daily doses of 0.5 or 1.0 g/kg body weight, 6 days each week, for 16 weeks. The psyllium formulation was mixed with a portion of the daily food. A 56 percent psyllium formulation was administered in doses of 1.0 g/kg body weight following a similar protocol. No significant differences were observed in body weight gains of treated and control groups, or in hematology, blood chemistry, and urinalysis of samples taken at 0, 8, and 16 weeks. The investigator reported that histological examination revealed no changes of importance in the heart, lungs, liver, spleen, kidneys, adrenals, thyroid, pancreas, testes, ovaries, or gastrointestinal tract.

In summary, results of short- and long-term feeding studies in mice, rats, and dogs suggest an absence of significant adverse effects. In some studies, dark pigmentation of the kidneys was reported; its origin was not determined, but renal function was not impaired.

2. Human studies

Thienes and Hall (1941) observed 9 persons who had taken 7-14 g psyllium-agar flakes daily for 2-7 years. Urea clearance tests and chemical analysis and microscopic examination of urine samples were within normal limits, and the authors reported no clinical evidence of kidney dysfunction. In a double-blind experiment, Spiller et al. (1979) studied effects of psyllium seed hydrocolloid, a cellulose-pectin mixture, or a placebo (corn syrup solids) in 50 healthy adults aged 25-65 years who were known to have low average daily fecal weights. The psyllium seed preparation consisted of 50 percent psyllium seed hydrocolloid and 50 percent glucose. Following a 14-day baseline period 12 subjects were given 20 g of the psyllium preparation daily for 20 days (intake of psyllium seed hydrocolloid 10 g/day or approximately 140 mg/kg/day). Feces were collected on the last 7 days of the baseline and experimental periods. A low-residue diet was fed throughout the study. Fecal calcium, magnesium, and nitrogen excretions did not differ significantly for subjects given either treatment or placebo. Hematologic and blood chemistry values were within normal limits and occurrence of flatulence, gastrointestinal cramping, abdominal fullness, nausea, urgency to eliminate, headache, tiredness, weakness, or hunger was similar for all groups.

Brydon et al. (1979) administered 30 g/day (approximately 210 mg/kg/day of psyllium hydrocolloid) of a preparation containing about 50 percent psyllium hydrocolloid (Metamucil®) for 3 weeks to 11 adult patients with uncomplicated gallstone disease. No changes were observed in concentration of lithocholic, chenodeoxycholic, deoxycholic, or cholic acids in bile or in bile acid-cholesterol ratios. In contrast, Beher et al. (1973) reported that administration of 12 g/day of psyllium hydrocolloid to 6 post-cholecystectomy patients for 6-29 days gradually increased the concentration of deoxycholate in the bile but had little or no effect on the concentrations of cholesterol and phospholipid in the bile.

Mazzola and Cappuccilli (1978) administered formulations of purified psyllium seed husk to 31 patients for the treatment of chronic constipation or bowel irregularity. The patients were hospitalized for a variety of illnesses. An average dose of 6.4 g of the formulation (3.6 g psyllium seed husk) was given three times daily. Treatment during hospitalization ranged from 11-59 days and during outpatient treatment from 15-59 days. Mean cholesterol level of 13 patients with hypercholesterolemia decreased from an initial level of 329 mg/dl to 239 mg/dl at the end of the treatment. Mean cholesterol level of the other 18 patients, 210 mg/dl, was not significantly changed by the treatment. No adverse changes attributable to treatment were observed in hematological indices (hemoglobin, red or white corpuscle count) or blood chemistry (glucose, urea, serum glutamic oxaloacetic transaminase [AST], serum glutamic pyruvic transaminase [ALT], bilirubin, or alkaline phosphatase).

Young (1981) reported to SCOGS (Select Committee on GRAS Substances, 1982) that "approximately 4 million people of the U.S. use a commercial pharmaceutical formulation of psyllium seed husk gum and 4 percent of these have taken 1-3 doses (containing about 1.8 to 5.3 g psyllium seed husk gum) daily for more than 20 yr". The level of exposure established as safe for over-the-counter drug use of psyllium for 1 week or less is approximately 428 mg/kg/day or about 20-25 g/day for adults (Food and Drug Administration, 1985). General Mills scientists have proposed an Acceptable Daily Intake for psyllium of 200 mg/kg (10-12 g/day) (Van Brunt et al., 1989).

Sölter and Lorenz (1983) reported a clinical safety and efficacy study of the laxation effects of a psyllium-containing bulk laxative. Seven-day trials involved 15 centers and 669 patients (266 males and 403 females) ranging in age from 13 to 90 years. Subchronic trials (up to 12 weeks) involved

3 centers and 139 patients (59 males and 80 females) ranging in age from 9 to 80 years. The standard dosage of psyllium was 2 tsp or 114 mg/kg/day based on a 70-kg individual. Reported side effects were gaseous distension, abdominal pain, and occasional diarrhea. These symptoms regressed over time and diarrhea could be controlled by dosage adjustment.

Stoy et al. (1993) recently reported similar gastrointestinal symptoms in 6 subjects consuming PSH and wheat bran containing R-T-E cereals over an 18-week period. Symptoms were classified as mild to moderate in 6 of 18 subjects.

Proctoscopy was conducted on a random sample of subchronic trial patients and revealed no macroscopic evidence of changes in the rectal mucosa. Microscopic examination of samples revealed normal rectal mucosa. Electrolyte levels (potassium, sodium, and calcium) were unchanged.

In addition, diarrhetic patients and patients with Crohn's disease were studied under a similar dosage regimen. No significant effects were observed in body weight, blood pressure, or biochemical parameters (total protein, ALT, AST, gamma-GT, alkaline phosphatase, sodium, potassium) of Crohn's disease patients. The results revealed no adverse effects associated with psyllium ingestion under the aforementioned experimental conditions, other than those transient episodes of gaseous distension and abdominal pain, which tended to subside as treatment was continued.

In summary, short- as well as long-term studies of the effects of orally administered PSH or PSH mucilloid in healthy human subjects, patients with chronic constipation, and patients with gallstones revealed no significant untoward responses except for transient episodes of gastrointestinal side-effects such as gas and abdominal cramps.

3. Carcinogenicity, mutagenicity, and reproductive effects

No reports of studies specifically designed to test PSH for carcinogenicity were found. In 13 reports of animal studies involving psyllium feeding in different species for periods of 5 months to lifetimes, tumorigenesis was not mentioned; however, these studies were aimed at other endpoints (Buth and Mehta, 1983; Carlson and Hoelzel, 1948; Costa et al., 1989a,b; McCall et al., 1992a,b; Mercatelli et al., 1979a,b,c; Paulini et al., 1987; Richter and Schneeman, 1990; Schneeman and Richter, 1990, 1993; Thienes and Hall, 1941).

Several studies have examined the effects of psyllium on the tumorigenicity of carcinogens. One study suggested an increase in carcinogenicity of 1,2-dimethylhydrazine dihydrochloride (DMH), in male Swiss mice fed Metamucil® in their diet, but not in females (Toth, 1984). Roberts-Anderson et al. (1987) questioned the validity of Toth's conclusions, noting that "Toth actually found a reduced incidence of colon tumors (8:50) in the Metamucil® and DMH group versus 19:50 in the DMH alone group." In their experimental study, Roberts-Anderson et al. (1987) fed rats a 10 percent psyllium diet for 22 weeks and intubated DMH weekly for 8 weeks. They concluded that psyllium reduced the tumorigenicity of DMH. Wilpart and Roberfroid (1987) fed male DMH-treated Wistar rats 5 and 15 percent psyllium in 5 and 20 percent weight/weight fat diets for up to 45 weeks. The psyllium product showed anticarcinogenic effects in terms of the incidence of intestinal and colonic tumors.

The induction of colon tumors in Fischer-344 rats following subcutaneous injections of azoxymethane (AOM) was studied in relation to the influence of high-fat, low-calcium diets containing 1, 4, or 8 percent weight/weight wheat bran, psyllium (PSH provided by the Kellogg Company), or combined wheat bran and psyllium. The rats were fed the experimental diets for 2 weeks, then received 2 AOM injections 1 week apart. Twenty-three weeks after the first injection, tumor incidence was assessed. Increasing dietary fiber from 1 to 8 percent reduced the number of tumors per group. There was no difference in protective effect of wheat bran or psyllium (Alabaster et al., 1993).

Some studies have shown that consumption of readily fermentable soluble fibers such as gums and pectin, is associated with increased tumor development in animals receiving doses of known carcinogens (Jacobs, 1989; Schneeman and Tietyen, 1994). Jacobs (1990) and Lupton et al. (1985) showed that addition of fiber to the diets of rats modified the colonic epithelial cell cycle; that is, the fraction of replicating cells increased as did differentiation of goblet and columnar cells. Jacobs et al. (1989) reported that rats fed psyllium fiber supplements exhibited acidified luminal contents and stimulation of colonic crypt growth in the distal colon. On the other hand, Sakata (1987) showed that SCFA inhibited epithelial proliferation in isolated rat cecal tissues in vitro.

Other investigators have suggested that the SCFA may exert a protective effect against colonic neoplasia. Cummings and Macfarlane (1991) reviewed several studies that showed a protective effect of butyrate against neoplastic processes in a variety of cell types including human colorectal cells. In addition, Sakata (1987) showed that butyrate can reversibly alter the in vitro properties of human colorectal cancer cell lines by prolonging doubling time and slowing growth rates.

The Expert Panel estimated that consumption of food products containing PSH might reasonably be expected to increase total dietary fiber intakes of adults in the United States by about 1.3 to 5.4 g/day. Whether this would result in a significant increase in SCFA production is questionable. Consequently, the possible relevance of these studies to human colon cancer is far from clear. However, their possible relevance may be of interest in view of current suggestions to increase consumption of soluble forms of dietary fiber as a means of reducing serum cholesterol and of managing diabetes.

SCOGS (Select Committee on GRAS Substances, 1982) found no information on the possible mutagenicity of psyllium seed husk gum, nor have studies of possible mutagenicity appeared subsequently. Short-term animal feeding studies including reproduction and teratogenicity studies have shown no adverse effects (Select Committee on GRAS Substances, 1982).

Table 11 lists examples of studies of toxicity and other biologic effects of psyllium. Three studies listed in Table 11 (but not treated in the text) compared the effects of different dietary fibers on cholesterol absorption and metabolism (Arjmandi et al., 1992; Redard et al., 1992; Vahouny et al., 1988). One study compared the effect of different fibers and aging on blood lipids, bowel histology, and pancreatic amylase activity (Schneeman and Richter, 1993), and two studies examined the effects of various fibers on growth and structure of the small bowel (Calvert et al., 1985; Sud et al., 1988) and small intestine enzyme activity (Calvert et al., 1985).

C. POSSIBLE ADVERSE REACTIONS

Three main categories of concern about consuming PSH are evident from the scientific literature: (1) possible malabsorption of vitamins and minerals, (2) gastrointestinal obstruction, and (3) allergic reactions.

1. Effects on vitamin and mineral absorption

Table 12 lists examples of studies on the influence of psyllium on vitamin and mineral absorption. Most studies have focused on mineral absorption; few reports were available on the effects of psyllium on vitamin absorption and metabolism. Abraham and Mehta (1988) examined the effects of 3-week psyllium supplementation on plasma total and LDL cholesterol concentrations, fecal steroid excretion, and lipid and carbohydrate absorption in healthy adults. Among other findings, retinyl esters quantitated after psyllium supplementation were not different from values during the control diet period. In another study, Roe et al. (1988) found that absorption of pharmacologic doses of riboflavin

Table 11. Biological Studies of Psyllium Seed Husk.*

SOURCE	TYPE OF STUDY	SUBJECTS	SUBSTANCE TESTED	DOSE AND ROUTE	DURATION	RESULTS AND COMMENTS
Schneeman and Richter, 1993	long-term study of DF and aging on lipids, bowel histology, and pancreatic enzymes	weanling male Wistar rats	PSH, WB, OB	40 g PSH per 960 g defined basal diet	3.5-18.5 mo	animals sacrificed after 3.5, 10, 15, or 18.5 mo on the test diets. Plasma Chol and PT ↑ at 18.5 mo compared with younger rats. DF did not prevent age-related ↑ in plasma and liver lipids except that liver Chol was not affected; pancreatic amylase ↓ with age in all groups; in PSH and OB groups cecal wt and ileal smooth muscle > in controls
Arjmandi et al., 1992	feeding trials to compare biologic effects of soluble fibers	Sprague-Dawley rats, 172-178 g	PSH added Chol	7.5% of diet 0.3% of diet	3 wk	rats fed added Chol: liver and serum Chol in PSH group > in pectin group; PSH group fecal neutral sterol > in cellulose controls; all groups had ↑ bile acid excretion compared with cellulose controls not given added Chol
Redard et al., 1992	feeding trial of DF and postprandial lipid responses	male Wistar rats 250 g	PSH, CL, OB	5g/100g of defined diet	4 wk	fasting plasma Chol and HDL-Chol in PSH group < in CL and OB groups; plasma PT ↑ in all groups; postprandial ↑ in HDL fraction in PSH group; in 12-h fasted animals, liver and intestine apo A-IV mRNA > in CL group; apo B mRNA > in OB group
Turley et al., 1991	a study to compare the effects of PSH, cholestyramine and surfomer on sterol metabolism	male Golden hamsters	PSH, cholestyramine, surfomer	7.5% of semi-synthetic diet	14-21 d	all 3 test agents lowered plasma total Chol and LDL-Chol; Chol synthesis ↑ in livers (but not other tissues) of PSH group; when Chol and saturated TAG added to diet, PSH feeding blocked ↑ in plasma and hepatic Chol levels; intestinal bile acid pool ↑ by PSH and cholestyramine and was readily absorbed in PSH animals

* See code for abbreviations at end of table.

Table 11. (continued).

SOURCE	TYPE OF STUDY	SUBJECTS	SUBSTANCE TESTED	DOSE AND ROUTE	DURATION	RESULTS AND COMMENTS
Sud et al., 1988	a study of DF and small intestine structure	weanling rats and hamsters	PSH, CL	PSH - 10g/100g defined diet CL - 10g/100g defined diet	>4 wk	increased length and weight of small intestine in PSH group > in CL group > in fiber-free diet group; mucosal thickness and villus height ↓ in proximal, but ↑ in distal small intestine; these changes were greater in the PSH group
Vahouny et al., 1988	subchronic study of fiber supplements and cholesterol absorption/metabolism	adult male rats	dietary fiber derivatives including PSH	10g/100g diet; oral	4 wk	After 4 wk, lymphatic catheters installed and animals starved overnight. Chol absorption ↓ at 24 h; absorption of oleic acid delayed but not ↓
Calvert et al., 1985	a study of DF and digestive enzyme activities	male Wistar rats, 200g	PSH, CL, alfalfa, pectin, guar gum	PSH 10g/100g defined diet	4 wk	proximal small intestine: invertase ↑ in CL, guar, PSH groups; alkaline phosphatase ↑ in alfalfa, guar, PSH groups; distal ⅗ of small intestine: thymidine kinase activity ↑ in guar and PSH groups; distal ⅕ of small intestine: mucosal proteins ↑ in PSH and guar groups; pancreatic enzyme activities were similar to those in control group
Mercatelli et al., 1979 a,b,c	chronic toxicity	6 beagles 3♂ 3♀	purified PSH	250 or 750 mg/kg/d; oral	6 mo	no significant effects on food consumption, body weight, hematology, renal or hepatic function, gross and microscopic anatomy of 31 organs and tissues; at 6 mo there were differences between controls and treated animals in serum total protein, lipids, glucose, inorganic P, Na^+, and K^+; however, these were apparently of no biologic consequence
Fraschini, 1978	acute toxicity	Swiss mice Sprague-Dawley rats	purified PSH (Metamucil®)	1.5, 3, 6 g/kg bw by gavage	7 d	sl sedation at 6 g/kg diarrhea in mice at 6 g/kg
Fraschini, 1978	subchronic toxicity	Sprague-Dawley rats	"powder" (49% PSH); "instant dose" (56% PSH)	0.5-1.0 g/kg bw by gavage 1.0 g/kg bw	6 d/wk for 25 wk	no gross, microscopic, hematologic, or biochemical changes attributable to the treatment

* See code for abbreviations at end of table.

Table 11. (continued).

SOURCE	TYPE OF STUDY	SUBJECTS	SUBSTANCE TESTED	DOSE AND ROUTE	DURATION	RESULTS AND COMMENTS
Fraschini, 1978	subchronic toxicity	4 beagles	49% PSH "powder" 56% PSH "instant dose"	0.5 g/kg bw 1.0 g/kg bw	6 d/wk 16 wk	no significant changes in body wt, hematology, urinalyses or blood chemistry except lower blood cholesterol
Coulston and Seed, 1956	subchronic study of renal effects	Sprague-Dawley rats	various fractions of P. ovata and P. arenaria	10% of the basal diet	28 wk	kidneys of rats fed tailings of PSH were grossly brownish, no microscopic pigment; appearance, weight gain, and behavior normal in all groups
Thienes and Hall, 1941	subchronic study of renal effects long-term human observations on renal effects	rats rats and kittens 9 human subjects	pulverized psyllium psyllium-agar/flakes (75%-25% respectively) psyllium-agar flakes	5% and 25% of basal diet 5% and 25% of basal diet 7 to 15 g/d	150 d 52 d 2 to 5 y	dark brown or black kidneys; pigment in renal tubules; urea clearance normal, no microscopic renal pigment normal urinalyses and normal PSP elimination
MacKay et al., 1932	subchronic study of G-I effects of dietary roughage	albino rats 6 young dogs	finely ground psyllium seed whole psyllium seed (2 dogs) ground psyllium seed (2 dogs)	25% of basal diet 25% of basal diet 25% of basal diet	125 d 30 d 30 d	renal tubule epithelium contained brown pigment; kidneys grossly black no renal pigment kidneys gray-black; no pigment granules on microscopic examination

CODE FOR ABBREVIATIONS IN TABLE 11

Chol	=	cholesterol	PSP	=	phenolsulfonphthalein
CL	=	cellulose	PT	=	plasma triglycerides
DF	=	dietary fiber	TAG	=	triacylglycerols
HDL-Chol	=	high density lipoprotein-Chol	tailings	=	PSH treated to remove mucilage fractions
mRNA	=	messenger ribonucleic acid	WB	=	wheat bran
OB	=	oat bran			
PSH	=	psyllium seed husk			

Table 12. Effects of Psyllium on Vitamin and Mineral Status.

SOURCE	DOSAGE	DURATION	SUBJECTS	RESULTS AND COMMENTS
ANIMAL STUDIES				
Lawrence et al., 1990	1-5% of diet supplemented with PSH	91 d	Fischer 344 rats	no apparent effect on Na and K status; urinary P and Mg ↓ as psyllium ↑; serum and bone Mg and P status unchanged; no apparent adverse effect on other mineral status
Jacobs and Domek, 1989	1-5% of diet supplemented with PSH	4 wk	Sprague-Dawley rats	hepatic and serum Cu ↑; hepatic and serum Zn unchanged; intestinal absorption of Zn and Cu unchanged
Jacobs et al., 1989	1-5% of diet supplemented with PSH	4 wk	Sprague-Dawley rats	fecal concentrations of Cu, Zn, Mg, Mn, Ca, and Fe were diluted dose-responsively; serum Cu levels increased while Mg, Zn, and Ca were unchanged; psyllium modifies intestinal mineral metabolism
Paulini et al., 1988	9.7% of diet supplemented with PSH	3 y (monkeys) 10 wk (rats)	African green monkeys, Sprague-Dawley rats	in monkeys, no effect on Zn status; serum Cu ↓; liver and kidney Cu unchanged; tibia Zn ↓ slightly in rats on marginal Zn intake; PSH had no adverse effect on Zn and Cu status with non-marginal diets
Vahouny et al., 1987	5% of diet supplemented with PSH	4 wk	Wistar rats	positive balances of intake vs. fecal output for Ca, Fe, Mg, and Zn
Mehta and Poetter, 1984	5-10% of diets supplemented with PSH	10 wk	weanling rats	with marginal Zn diet, slight effect on tibia Zn, but none on absorption
Buth and Mehta, 1983	9.7% of diet supplemented with PSH	16 mo	African green monkeys	Fe utilization increased and fecal loss decreased
Mercatelli et al., 1979a,b,c	250-750 mg PSH/kg/d	6 mo	beagles	serum P ↑ at 250 mg/kg dose; Na and K ↑ in ♀ at 750 mg/kg dose
Fraschini, 1978	0.5-1.0 g/kg/d of PSH	25 wk	Sprague-Dawley rats	no changes in hematological, hematochemical, and urine values

Table 12. (continued).

SOURCE	DOSAGE	DURATION	SUBJECTS	RESULTS AND COMMENTS
Salerno et al., 1978	800 mg/kg/d of PSH	15 d	beagles	no changes in blood biochemistry
HUMAN STUDIES				
Levin et al., 1990	10.2 g/d of Metamucil®	16 wk	96 ♂ and ♀	no significant differences in indicators of vitamin K status
Ganji and Kies, 1990	not reported	10 d	25 subjects sex not reported	Zn balance not adversely affected by combined intake of psyllium and Fe supplements
Bell et al., 1989	10.2 g/d of Metamucil®	8-16 wk	38 ♂, 37 ♀	no effect on serum Fe levels
Anderson et al., 1988	10.2 g/d of Metamucil®	8 wk	26 ♂	no effect on serum levels of Fe and Zn
Abraham and Mehta, 1988	300 mg/kg/d PSH	3 wk	7 ♂	no effect on fecal steroid excretion or levels of plasma triglycerides, retinyl esters, glucose, insulin, and glucagon quantitated during meal tolerance tests
Roe et al., 1988	2.3-5.7 g of PSH/d	1 d	12 ♀	reduced absorption of pharmacological doses of vitamin B_2
Gillooly et al., 1984	5 g of Mucilose	1 d	6 ♀	Fe absorption decreased
Rampton et al., 1984	7 g/d	9 wk	1 uremic pt	fecal excretion of N, K, Ca, and Mg increased while that of P decreased: no apparent effects on plasma P, Ca, and K
Sölter and Lorenz, 1983	2 tsp Prodiem/d (active ingredient is PSH)	7 d - 12 wk	266 ♂, 403 ♀	no significant effect on serum Na and K levels
Kies, 1983	14-20 g PSH/d	not specified	not specified	increased fecal loss of Cu, Zn, Ca, and Mg
Burton and Manninen, 1982	up to 25 g PSH/d	16 wk	6 ♂, 6 ♀	serum Ca ↓ after PSH supplement stopped; serum Fe unchanged
Enzi et al., 1980	6 g PSH/d	30-150 d	22 ♀	plasma Fe and Ca levels ↓ slightly during first 30 d, but stabilized thereafter

Table 12. (continued).

SOURCE	DOSAGE	DURATION	SUBJECTS	RESULTS AND COMMENTS
Spiller et al., 1979	20 g PSH/d	21 d	50 ♂ and ♀	fecal excretion of Ca and Mg unchanged; no abnormal changes in plasma chemistry
McHale et al., 1979	10-20 g/d of PSH-derived hemicellulose	21 d	9 ♂, 3 ♀	serum Ca unchanged; serum Mg ↓ at 20 g dose
Drews et al., 1979	14.2 g/d of PSH-derived hemicellulose	4 d	8 young boys	fecal excretion of Zn, Fe, and Mg ↑
Kies et al., 1979	4.2, 4.2, and 24.2 g/d, 14 d at each dose, PSH-derived hemicellulose	50 d total	12 ♂	fecal Zn ↑ in dose-dependent manner; no effect on serum and urine Zn
Giovannini and Careddu, 1978	3.6 g/d of PSH	10-14 d	humans	no changes in mean values of blood chemistry parameters
Davi and Strano, 1978	7 g/d of PSH	10 d	humans	no changes in hematological parameters
Kies and Fox, 1976	8 or 23 g/d of hemicellulose derived from PSH	42 d total	41 ♂ and ♀	fecal Zn excretion ↑ with high dose of hemicellulose

in subjects given a test meal containing 7.5 g psyllium decreased from about 32 percent to about 25 percent ($P < .01$).

In studies of the effects of a daily supplement of 5.1 g PSH in hypercholesterolemic patients, Levin et al. (1990) included measurement of prothrombin time and partial thromboplastin time. These indicators of changes in vitamin K absorption did not differ between the PSH-fed and the control groups. Testimony before the Select Committee on GRAS Substances (Young, 1981) included an estimate that approximately 4,000,000 people in the United States had used psyllium-containing bulk laxatives safely; of these, approximately 160,000 had taken 1 to 3 doses (containing ~1.8 - 5.3 g PSH) daily for more than 20 years. These 160,000 consumers were not subjects of any epidemiologic surveys of vitamin status. The Expert Panel discovered no reports of possible avitaminosis that could be attributed to consumption of PSH.

In summary, there is a paucity of reports of studies designed to assess the possible effects of PSH on vitamin absorption; however, the absence of reports of effects of long-term consumption of psyllium-containing laxatives suggests that this possibility is minimal.

In addition, Table 12 lists 10 animal and 16 human studies that included data on mineral absorption and metabolism. Seven of the animal studies and nine of the human studies reported some effect of PSH or purified hemicellulose derived from PSH on minerals; the remaining three animal studies (Fraschini, 1978; Salerno et al., 1978; Vahouny et al., 1987) and human studies (Davi and Strano, 1978; Giovannini and Careddu, 1978; Sölter and Lorenz, 1983; Spiller et al., 1979) reported no effects on minerals.

Of the animal studies that revealed some influence of psyllium on minerals, the reported effects were trivial in one (Lawrence et al., 1990) and, in two studies, significant only when dietary intakes were marginal (Mehta and Poetter, 1984; Paulini et al., 1988). Jacobs and Domek (1989) reported that the increased levels of serum and hepatic Cu in their rats may reflect a mechanism (unspecified) by which psyllium lowers serum cholesterol levels. Jacobs et al. (1989) had no explanation for increased serum Cu levels in their PSH-supplemented rats.

In their long-term study of the effects of a PSH-supplemented diet in African green monkeys, Buth and Mehta (1983) ascribed the observed decreased fecal loss and increased metabolic utilization of Fe to the effect of psyllium in prolonging intestinal transit time. Mercatelli et al. (1979a,b,c) reported increases in serum P, Na, and K in beagles fed PSH for 6 months. There were no associated physiological or histopathological abnormalities.

In a series of human studies, Kies and associates reported increases in fecal and urinary mineral losses and altered mineral absorption in 5 separate investigations (Drews et al., 1979; Kies, 1983; Kies and Fox, 1976; Kies et al., 1979; McHale et al., 1979). In general, these studies suggested that, with adequate dietary intakes of minerals, the reported alterations were of no physiologic significance; however, caution was recommended against overuse of fiber supplements in circumstances where dietary intakes of minerals are marginal or inadequate.

Gillooly et al. (1984) concluded from a study of Indian women in South Africa that hemicellulose derived from PSH may act as an inhibitor of Fe absorption compared with cellulose. Serum Ca levels decreased in subjects following 16 weeks' treatment with PSH for constipation (Burton and Manninen, 1982). The authors had no explanation for this phenomenon. Enzi et al. (1980) found slight but significant decreases in plasma Fe and Ca levels during the first 30 days of treatment of obese patients with an 800 kcal diet plus 6 g PSH/day. Further decreases in Fe and Ca did not occur when treatment was continued beyond 30 days (up to 6 months in some patients).

The results of the animal and human studies on the influence of PSH on mineral absorption and metabolism suggest that, at psyllium intakes contemplated for its use as a food ingredient, no significant adverse effects would be likely unless dietary intakes of minerals were marginal.

2. Gastrointestinal and esophageal obstruction

Bowel or esophageal obstruction associated with psyllium ingestion has occurred almost exclusively in individuals with existing intestinal or esophageal abnormalities who ingested psyllium in bulk laxatives without proper hydration (Van Brunt et al., 1989). Data from published case reports are shown in Table 13. There are no reports of gastrointestinal or esophageal obstruction associated with consumption of Heartwise®, which, according to the Kellogg Company, is intended to be consumed with milk and in which the PSH is already partially hydrolyzed in the production process (Fulgoni, 1993a; Furth et al., 1989c).

On the other hand, during the period 1980-1988, there were 61 episodes of esophageal obstruction associated with use of the bulk laxative Perdiem®. Perdiem® is 82 percent psyllium and 18 percent senna. Whether or not water was taken with the Perdiem®, as recommended by the manufacturer, was not reported in all but 13 of the 61 cases. Of these 13 cases, 5 patients took a full glass, 7 took a little or an insufficient amount, and 1 took none. Twenty-nine of the sixty-one patients reported pathologic, anatomic, or functional abnormalities of the esophagus (Gilbertson, 1990). The FDA has recently published regulations on warning statements for over-the-counter bulk laxatives containing water soluble gums such as PSH (Food and Drug Administration, 1993a).

No data are available on the question of possible alimentary tract obstruction that could be associated with future consumption of PSH-containing products such as poptarts, waffles, breads, rolls, and muffins. While moderate amounts of PSH contained in those products would not be expected to cause gastrointestinal obstruction, this possibility would be reduced by suitable suggestions that these products be consumed with fluids such as milk, cocoa, coffee, tea, juice, soft drinks, or water.

3. Allergenicity

As of March 1991, 32 clinical or epidemiologic reports of psyllium sensitivity were published (Table 14). Most of the reported individuals were nurses or pharmaceutical workers apparently sensitized by occupational exposure to psyllium by inhalation rather than ingestion. Reactions have been reported both after inhalation and after ingestion of psyllium-containing products. The severity of reported reactions ranged from relatively mild episodes to life-threatening anaphylaxis. Symptoms described included rhinitis, sneezing, wheezing, dyspnea, conjunctival pruritus, lacrimation, urticaria, angioedema, gastrointestinal distress, hypotension, tachycardia, and anaphylaxis. In many subjects IgE-mediated sensitivity to psyllium was demonstrated by skin testing, passive transfer, radioallergosorbent testing, or inhalation or oral challenge.

In 1990, two cases of anaphylaxis following the ingestion of Heartwise® cereal were reported (Kaplan 1990; Lantner et al., 1990). Both women were nurses who had been exposed to psyllium by dispensing psyllium-containing bulk laxatives to patients. They had not experienced symptoms upon exposure to psyllium at work and did not previously consider themselves to be psyllium-sensitive. In 1991, James et al. described their evaluation of 20 of 24 cases of allergic reactions to psyllium-containing cereals reported to the Kellogg Company between August 1989 and March 1990. All 20 of the subjects were women and 14 were nurses. Three of the six women who were not nurses had either dispensed or taken psyllium-containing laxatives. Eleven of the fifteen women who had dispensed psyllium-containing products had experienced allergic symptoms while dispensing psyllium prior to their reaction caused by psyllium ingestion. Eighteen of the women were atopic.

TABLE 13. Case Reports of Gastrointestinal and Esophageal Obstruction Associated with Ingestion of Psyllium-containing Bulk Laxatives.

AUTHOR	LOCATION OF OBSTRUCTION	LAXATIVE USED	ASSOCIATED FACTORS
Roden, 1951	esophagus	Serutan®	patient took 2 tsp dry Serutan® with 1 glass water
Hinkel, 1951	esophagus	Serutan®	hiatal hernia; patient took two 2 tsp dry Serutan® with 1 glass water
Melamed and Marck, 1953	esophagus	Serutan®	history of subtotal gastrectomy and limited food intake capacity; took 2 tsp dry Serutan® with "swallow of water"
Johnson, 1953	esophagus	Serutan®	"minimal hiatal insufficiency"; put 2 tsp dry Serutan® in glass of water and swallowed immediately
Lyall and Akey, 1957	cecum and ascending colon	Serutan®	Serutan® accumulated in cecum and ascending colon proximal to an annular carcinoma; enemas resulted in excess water in proximal colon and enormous swelling of the Serutan®
Souter, 1965	three cases: 1. cecum and ascending colon 2. hepatic flexure and proximal transverse colon 3. ascending colon	I-so-gel®	1. perforated diverticulitis treated by coloscopy; I-so-gel® given to control diarrhea 2. diverticulitis treated by colostomy; I-so-gel® given to control diarrhea 3. fecal fistula treated by colostomy; I-so-gel® given to control diarrhea
Berman and Schultz, 1980	throughout small intestine	bulk laxative	patient took excessive doses over a long period of time
Noble and Grannis, 1984	esophagus	Perdiem®	history of mild episodic dysphagia; patient took "heaping" tsp with "some" water
Agha et al., 1984	right colon	unrefined PSH	history of chronic constipation and consumption of large amounts of vegetable pulp
Olinde and Maher, 1986	mid-ileum	psyllium hydrophylic mucilloid	history of subtotal gastrectomy; took 2 tbsp psyllium twice daily
DiPalma and Brady, 1987	esophagus	Perdiem®	took 1 tbsp Perdiem® mixed with water

TABLE 14. Survey of Clinical and Epidemiological Reports of Psyllium Sensitivity.

AUTHOR, YEAR, COUNTRY	EXPOSURE	FINDINGS
Ascher, 1941 USA	1 pharmacy worker	rhinitis and gastrointestinal allergy; skin test positive
Bernton, 1970 USA	1 psyllium handler (dispenser to spouse)	asthma
Busse and Schoenwetter, 1975 USA	3 pharmacy workers	asthma, wheezing, sneezing, itching; skin test positive in all; bronchial provocation (BPC) positive in 2
Göransson and Michaelson, 1979 Sweden	27 pharmacy workers 5 nurses who dispense psyllium	asthma, rhinitis, conjunctivitis; BPC positive
Machado, Zetterström, and Fagerberg, 1979 Sweden	2 nurses who dispense psyllium 8 pharmacy workers	rhinitis, sneezing, and skin and eye irritation with positive skin and/or radioallergosorbent (RAST) tests
Gross, 1979 USA	1 nurse who dispensed psyllium 2 others who reported similar symptoms	asthma, wheezing, shortness of breath
Nelson, 1980 USA	1 user	eosinophilia
Terho and Torkko, 1980 Finland (as cited in Suhonen et al., 1983)	2 nurses who dispensed psyllium	asthmatic reactions; positive skin and RAST tests
Zetterström et al., 1981 Sweden	9 pharmacy workers (survey)	positive RAST tests
Rosenberg et al., 1982 USA	1 pharmacy worker	coughing, wheezing, shortness of breath; positive RAST and skin tests
Machado et al., 1983 Sweden	6 nurses 9 pharmacy workers	rhinitis, wheezing, shortness of breath, itching; positive RAST and skin tests

TABLE 14. (continued).

AUTHOR, YEAR, COUNTRY	EXPOSURE	FINDINGS
Suhonen, Kantola, and Bjorksten, 1983 Finland	1 nurse who dispensed psyllium	anaphylactic shock from ingestion; positive RAST and skin tests
Machado and Stalenheim, 1984 Sweden	6 nurses who dispensed psyllium	respiratory problems and gastrointestinal symptoms following ingestion; positive RAST and skin tests
Zaloga, Hierlwimmer, and Engler, 1984 USA	1 nurse who dispensed psyllium	anaphylaxis, facial swelling, urticaria, wheezing following ingestion; positive RAST and skin tests
Seggev, Ohta, and Tipton, 1984 USA	1 nurse who dispensed psyllium	hypotension, wheezing, and urticaria following ingestion; positive RAST and skin tests
Gauss, Alarie, and Karol, 1985 USA	1 pharmacy worker	wheezing, sneezing, shortness of breath, itching, dermatitis; RAST test positive
Schoenwetter, 1985 USA	2 nurses who dispensed psyllium	rhinitis, laryngeal edema, hypotension, asthmatic symptoms; skin and RAST tests positive
Drewes, 1985 Sweden	1 pharmacy worker	asthmatic symptoms; positive skin and RAST tests
James et al., 1991 USA	20 women reporting reactions to Heartwise® 14 nurses and 3 who had dispensed or used bulk laxatives	wheezing, chest tightness, urticaria
Arlian et al., 1992 USA	11 psyllium RAST-positive individuals who submitted to experiments	IgE reactive bands detected; found contaminating seed components other than psyllium seed husk itself caused reactions
Marks et al., 1991 Australia	125 pharmaceutical workers given skinprick tests	7.6 percent tested allergic to psyllium; IgE-mediated allergic response mechanism deemed present

To demonstrate immunologic sensitization of the subjects to psyllium, James et al. (1991) extracted protein fractions from the psyllium-containing cereal as well as from psyllium mucilloid and the psyllium-containing bulk laxative, Metamucil®. A number of protein fractions ranging from 12 to 66 kilodaltons were identified in the extracts. Immunoblotting techniques were used to demonstrate the presence of IgE and IgG antibodies to psyllium antigens in the sera of the subjects. In an attempt to remove the allergenic portion of crude psyllium, psyllium powder was mechanically purified by passage through a series of mesh screens, and the retained material was found to contain less allergenic material. James et al. (1991) concluded that individuals sensitized by occupational exposure to psyllium dust are at high risk for allergic reactions to ingested psyllium-containing products. They suggested that increasing the purity of the psyllium mucilloid powder might result in a decrease in the allergenicity. However, studies using PSH preparations of higher purity to challenge known psyllium-sensitive individuals have not been performed under controlled conditions to confirm this.

Sixty-two allergic reactions were reported between August 1989 and May 1990. During this time about 6.08 million packages of Heartwise® were produced yielding a rate of 10.2 reactions per million packages. In June 1990 the Kellogg Company increased purity of the PSH used in the preparation of Heartwise® from 85 to 95 percent. Three allergic reactions were reported and about 4.25 million packages of the reformulated Heartwise® (Fiberwise®) were produced from June 1990 to September 1992, yielding a rate of 0.7 cases per million packages. However, in the summer of 1990, Kellogg also added an information statement on its packaging for Heartwise® which read:

> "NEW USERS: A very small percentage of individuals, particularly some nurses and other health care providers who have been occupationally exposed to psyllium dust, may develop a sensitivity to psyllium. This sensitivity may result in an allergic reaction."

Thus, although the number of reported reactions decreased after the reformulation, it is difficult to discern whether the decrease in reported reactions resulted from the reformulation, the warning label, both, or neither.

Using purer preparations of psyllium seed husk and adding warning labels might lead to fewer allergic reactions to psyllium-containing, ready-to-eat breakfast cereals. However, isolated reactions, including anaphylaxis, would be expected to occur in extremely sensitive individuals unless all of the allergen were removed. A lower limit of exposure that is safe for exquisitely sensitized individuals who might have anaphylactic reactions has not been determined.

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V. OPINION OF THE EXPERT PANEL

A. CONCLUSIONS

Psyllium seed husk (PSH) contains a mucilaginous polysaccharide that is a highly branched acidic arabinoxylan. The predominant monosaccharide components are D–xylose and L-arabinose. PSH as a product of commerce is derived from *Plantago ovata* and related species grown primarily in India and other subtropical and temperate regions. The mucilage derived from the seed husk has been used for food, feed, and as a bulk laxative for many years.

This report concerns the safety of a PSH product proposed for use as a food ingredient in grain-based foods by the Kellogg Company. The Kellogg PSH is blond psyllium derived from *P. ovata* seed grown in India, imported into the United States by J.B. Laboratories, Inc., and further refined by them and the Kellogg Company prior to use. According to the information received from the Kellogg Company, the product for which they seek Generally Recognized as Safe (GRAS) status is PSH, not PSH gum; however, the gum or mucilage itself is contained within the husk and the product of interest is at least 95 percent pure PSH, containing about 85 percent arabinoxylan gum and 15 percent nonpolysaccharide plant cell and cell wall material.

In 1982, the safety of PSH gum was considered by the Select Committee on GRAS Substances. The Select Committee stated:

> "Psyllium seed husk gum has been widely used in this country as a bulk laxative since approximately 1930. The acute toxicity of the gum is very low. Short-term animal feeding studies, including reproduction and teratogenicity studies, have demonstrated no adverse effects. Clinical studies on the effect of the gum on bowel action have revealed no significant side effects. There are no official specifications for a food-grade product and little, if any, appears to be used as an ingredient in processed foods."

Based on the evaluation of scientific data and information available at that time, the Select Committee concluded:

> "There is no evidence in the available information on psyllium seed husk gum 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 the future."

However, since that time, various food uses of the psyllium mucilloid have been reported. Two manufacturers, the Kellogg Company and General Mills, Inc., petitioned the FDA for GRAS status of an 85 percent pure PSH product in 1989. The GRAS petitions of both companies note little use in foods at that time (1989) but cite and document a long history of use of psyllium seed, PSH, and PSH gum as foods and beverages in several countries throughout the world.

The Kellogg Company requested that the Expert Panel evaluate the available information and data on safety of the recently modified PSH product, derived from psyllium seed by a modified extraction process which yields a 95 percent pure PSH product. The Kellogg Company proposes to use this product in various grain-based foods as a food ingredient in the following concentrations and types of foods: 15 percent by weight in ready-to-eat cereals, 10 percent in breakfast bars, and 7.5 percent in bread-based products and pasta.

The Expert Panel has established that consumption of one food item containing PSH on a single eating occasion would result in mean intakes ranging from 1.9 to 5.3 g per eating occasion for 1- to 2-year-old children and 4.0 to 12.1 g for 15- to 18-year-old males. For 90th percentile consumers, intakes would range from 3.8 to 11.0 g per eating occasion for 1- to 2-year olds and from 7.5 to 21.9 g per eating occasion for 15- to 18-year-old males.

On the basis of usual consumption, consumption of one item containing PSH would result in mean intakes of 0.7 to 2.7 g/day for 1- to 2-year-old children and 1.3 to 5.4 g/day for 15- to 18-year-old males. For 90th percentile consumers, PSH intake from one food item would range from 1.3 to 5.7 g/day for 1- to 2-year-old children and 2.7 to 11.3 g/day for adolescent males.

Incorporation of PSH into cereals would probably not increase total fiber intake appreciably, assuming that PSH replaces other fiber sources in cereals and that individuals consume the same size servings of cereals containing PSH as they do of other cereals. However, addition of PSH to products that have not previously contained appreciable amounts of fiber could add a mean intake of 1.3 to 5.4 g of PSH per day for adolescent males consuming a single product from only one food category. Persons in the various age/sex categories who usually consume ready-to-eat cereals could consume 1.7 to 5.4 g/day of PSH on the basis of mean intakes and as much as 11.3 g/day for the 90th percentile eaters. The Expert Panel also found it reasonable to expect that persons preferentially consuming products containing PSH might ingest about 25 g/day of PSH. Total dietary fiber intake is estimated to range from 11 to 20 g/day for adults and comes from multiple sources. Based on the estimated intake of PSH by 15- to 18-year-old males, consumption of mean amounts of foods containing PSH might reasonably be expected to increase total dietary fiber intake by about 1.3 to 5.4 g/day for adults in the United States.

In reviewing the information and data on safety of the PSH product, the Expert Panel concluded that despite differences in processing methodology, the information and data on PSH gum, while limited, is relevant to the safety of the PSH product of the Kellogg Company because its major component is the mucilloid arabinoxylan polysaccharide component extracted from the seed husk.

Psyllium seed husk appears to have no nutritional value but exerts a bulk-forming and lubricant effect on intestinal contents. Animal and human studies indicate it is nontoxic, as does its long history of safe use as an over-the-counter bulk laxative. There have been numerous studies of the consequences of consumption of various forms of psyllium mucilloid; however, data on safety are fragmentary.

For example, few studies have focused on possible effects on vitamin absorption; however, there are no anecdotal or clinical observations of possible effects from a long history of use of psyllium-containing laxatives. While there have been several studies on the effects of psyllium consumption on mineral absorption and metabolism, the data suggest that, at psyllium intakes contemplated for use as a food ingredient, no significant adverse effects would be likely unless consumption of dietary minerals was marginal.

Results of short- and long-term feeding studies in mice, rats, and dogs suggest an absence of significant adverse effects from consumption of various forms of psyllium. An exception may be the observation in rats that the SCFA from fermentation of soluble fibers, including PSH, stimulate growth of colonic epithelium. The significance of this observation and its relevance to the safety of consuming soluble fiber are unclear. In addition, in some studies, dark pigmentation of the kidneys was reported, but renal function was not impaired. Short- as well as long-term studies of the effects of orally-administered PSH or PSH mucilloid in healthy human subjects, patients with chronic constipation, and patients with gallstones, revealed no significant untoward responses except for transient episodes of gastrointestinal side effects such as gas and abdominal cramps.

Some instances of esophageal and intestinal obstruction have been reported when PSH was ingested without adequate fluid. While the moderate amounts of PSH that are contemplated for use in poptarts, bread-based products, breakfast bars, pasta, and R-T-E cereals would not be expected to cause gastrointestinal obstruction, this possibility would be reduced by suitable suggestions that these products be consumed with fluids such as milk, cocoa, coffee, tea, juice, soft drinks, or water.

The most significant untoward reaction to ingestion of PSH has been allergy, usually in persons who were occupationally sensitized by PSH dust. As of March 1991, 32 clinical or epidemiologic reports of psyllium sensitivity were published. Reactions have been reported both after inhalation and after ingestion of psyllium-containing products. The severity of reactions ranged from relatively mild to life-threatening anaphylaxis. In many subjects, IgE-mediated sensitivity to psyllium has been demonstrated by skin testing, passive transfer, radioallergosorbent testing, or inhalation, or oral challenge. In 1991, 20 of 24 cases of allergic reactions to psyllium-containing cereals reported to Kellogg between August 1989 and March 1990 were evaluated in a series of clinical investigations. Eleven of the fifteen women who had dispensed psyllium-containing products had experienced allergic symptoms while dispensing psyllium prior to their reactions caused by psyllium ingestion. Eighteen of the women were atopic. Protein fractions from the psyllium-containing cereal as well as from psyllium mucilloid and the psyllium-containing bulk laxative, Metamucil®, were extracted to demonstrate immunologic sensitization of the subjects to psyllium. Immunoblotting techniques demonstrated the presence of IgE and IgG antibodies to psyllium antigens in the sera of the subjects.

In June 1990 the purity of the PSH used in the preparation of Heartwise® was increased from 85 to 95 percent. Prior to that time, the rate of reactions was 10.2 per 1 million packages of Heartwise®. From June 1990 to September 1992, 95 percent PSH was used in the reformulated cereal, and the rate of reactions dropped to 0.7 per million packages. However, in the summer of 1990, Kellogg added a warning label about possible allergic reactions on its packaging for Heartwise®. Thus, although the number of reported reactions decreased after the reformulation, it is difficult to determine conclusively whether the decrease in reported reactions resulted from the reformulation, the warning label, both, or neither.

To place the issue of allergenicity in perspective, the Expert Panel considered psyllium allergy in relation to other food allergies such as peanut and grain allergies. Fatal and nonfatal anaphylaxis has been reported in people who are hypersensitive to peanuts; however, such reactions to other grains, with the exception of wheat gluten are extremely rare. The available data suggest that the 95 percent pure PSH is less allergenic than the 85 percent product that was used formerly.

Based upon all the evidence considered, the Expert Panel concludes that:

> *There is no evidence in the available information on PSH that demonstrates or suggests reasonable grounds to suspect a hazard to the public when it is used in a number of food categories and at levels of addition that would result in total consumption of as much as 25 g/day of PSH. However, it is not possible to determine without additional data whether a significant increase in consumption above 20 to 25 g/day would constitute a dietary hazard. In making this conclusion, the Expert Panel is not endorsing the consumption of high levels or a single source of dietary fiber nor the use of fiber as a supplement in foods that are otherwise low in fiber.*

B. RECOMMENDATIONS

The Expert Panel has reviewed most critically the reports of and investigations on allergic reactions to PSH by a small, but identifiable, segment of the U.S. population. The Kellogg Company has addressed this issue by development of a PSH product of higher purity (95 percent) and use of warning labels to sensitive persons on ready-to-eat cereal packages. Using purer preparations of PSH and adding warning labels appear to have led to fewer allergic reactions to psyllium-containing, ready-to-eat breakfast cereals. However, isolated reactions, including anaphylaxis, would be expected to occur in extremely sensitive individuals unless all of the allergen were removed. Determination of a lower limit of exposure that is safe for exquisitely sensitized individuals has not been investigated.

Based on these considerations, the Expert Panel recommends that the Kellogg Company continue to label PSH-containing products appropriately in order to alert psyllium-sensitive individuals and that, in due course, additional studies be undertaken to determine the lower limit of exposure for psyllium-sensitive individuals.

Further, the Expert Panel recommends that if PSH is marketed for its proposed uses, a mechanism should be provided for consumer comment via labeling information. Consumer comments to the manufacturer, which are also made available to the Food and Drug Administration, would provide an additional follow-up measure to the assurance of safety evidenced by the information and data evaluated by the Expert Panel.

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APPENDIX

GLOSSARY

Apparent digestibility	the balance between intake of unavailable carbohydrate and its loss in feces when the balance is expressed as a fraction of unavailable carbohydrate intake (Livesey, 1990)
Atopy/atopic	a genetically determined disorder featuring an increased capacity to form reagin (IgE) antibodies and to acquire certain allergic diseases, especially asthma, hay fever, urticaria, and atopic dermatitis
Commercial grades of PSH	85 to 95 percent pure PSH
Isapgol	Common name for *Plantago ovata* and the derived mucilloid product
Ispaghula husk	the same as PSH
NIDDM	non-insulin-dependent diabetes mellitus
Plantago ovata	the plant from which PSH is derived
PSH (psyllium seed husk)	the seed coat (epidermis) of *Plantago ovata*; the epidermis is composed of large cells with transparent walls and filled with mucilage (the product used by the Kellogg Company in grain-based products)
Psyllium	as used in this report, a generic term for all *Plantago* species and the derived mucilaginous products
Psyllium mucilloid	a fiber obtained by extraction with cold or hot water from the seed husk of plants of the genus *Plantago*
Psyllium seed husk gum	the mucilaginous, principal component of PSH (85 percent mucilage polysaccharide plus lesser amounts of D-xylose and D-arabinose and small amounts of other monosaccharides) and 15 percent non-polysaccharide components
Psyllium seed husk powder	finely ground PSH
Purified psyllium mucilloid	a white, fibrous, slowly hydrating material that forms a clear gelatinous mass at 2 percent in water