NEW DIETARY INGREDIENT NOTIFICATION INFORMATION

I. Manufacturer

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The name of this new dietary ingredient is psyllium hemicellulose, the soluble fiber component of psyllium husk. As required in 21§CFR190.6(b)(2), the Latin binomial name (including author) of any herb or other botanical has been confirmed as provided in the National Center for Biotechnology Information located at :http://ncbi.nlm.nih.gov. NCBI Entrez Taxonomy Database for *Plantago ovata* is as follows:

***Plantago ovata* Forsk.**
Taxonomic Serial No.: 504438

Kingdom:	Plantae
Taxonomic Rank:	Species
Synonym(s):	Plantago brunnea Morris

Plantago fastigiata Morris

Plantago gooddingii A. Nels. & Kennedy

Plantago insularis Eastw.

Plantago insularis var. fastigiata (Morris) Jepson

Plantago insularis var. scariosa (Morris) Jepson

Plantago minima A. Cunningham

Common Name(s): desert Indianwheat

Taxonomic Status:

Current Standing: accepted

Data Quality Indicators:

Record Credibility Rating: verified - standards met

Kingdom	Plantae -- Planta, plantes, plants, Vegetal
Subkingdom	Tracheobionta -- vascular plants
Division	Magnoliophyta -- angiospermes, angiosperms, flowering plants, phanérogames, plantes à fleurs, plantes à fruits
Class	Magnoliopsida -- dicots, dicotylédones, dicotyledons
Subclass	Asteridae
Order	Plantaginales
Family	Plantaginaceae -- plantains
Genus	Plantago L. -- Indianwheat, plantain
Species	Plantago ovata Forsk. -- desert Indianwheat

Expert(s):

Expert: John Kartesz

Notes: Biota of North America Project (BONAP), University of North Carolina

Reference for: Plantago ovata

Other Source(s):

Source: The PLANTS Database, database (version 4.0.4)

Acquired: 1996

Notes: National Plant Data Center, NRCS, USDA. Baton Rouge, LA 70874-4490 USA. http://plants.usda.gov

Reference for: Plantago ovata

Source: The PLANTS Database, database (version 5.1.1)

Acquired: 2000

Notes: National Plant Data Center, NRCS, USDA. Baton Rouge, LA 70874-4490 USA. http://plants.usda.gov

Reference for: Plantago ovata

Publication(s):

Author(s)/Editor(s):

Publication Date:

Article/Chapter Title:

Journal/Book Name,

Vol. No.:

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Publisher:

Publication Place:

ISBN/ISSN:

Notes:

Reference for:

Geographic Division: North America

Jurisdiction/Origin: Continental US, Native

The Procter and Gamble Company (P&G) plans to manufacture this ingredient at their facility in Phoenix, AZ. The ingredient is psyllium hemicellulose that meets the specifications of the USP Monograph. Details of the ingredient, its manufacture and supportive safety and efficacy data follow.

II. Chemical Identification, Manufacture and Product Analysis

Chemical Name

Psyllium Hemicellulose

Nomenclature

Throughout its development history, psyllium hemicellulose has been identified generically as "Fraction B", "Fraction BC" or "Marlett". These generic descriptions are used in several of the source documents that appear in this review. In all of these instances, the generic description refers to the material we call psyllium hemicellulose.

Chemical Abstracts Service Registry Number

9034-32-6

Structural Formula

Proposed Formula-"Primary Structure of arabinoxylans of ispaghula husk and wheat bran." Proceedings of the Nutrition Society (2003), 62: 217-222.

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IV. Dietary Supplement Form, Conditions of Use, Specifications and Proposed Mechanism of Action

Product Form

The final product is a fine, odorless powder. The powdered form will be supplied as a dietary supplement in the recommended dosage amount of 2.5 grams of psyllium hemicellulose up to three times a day. The directions for use will be as follows: One heaping TEASPOON in 8 ounces of water up to three times daily. Under 6 yrs: Consult a doctor. NOTICE: Mix this product with at least 8 oz (a full glass) of water. Taking without sufficient liquid may cause choking. Do not take if you have difficulty swallowing.

Product Composition

Psyllium hemicellulose is a USP material. It is controlled lot-to-lot by testing according to the USP (Pharmacopeial Forum, Vol.30 (1), Jan.-Feb.2004) specifications described above. Following extraction, pasteurization, neutralization, dehydration and drying, the psyllium hemicellulose is chemically unchanged from its natural state in *Plantago ovata* as has been shown above.

Dietary Supplement Conditions of Use/Labeling

The recommended daily intake will be 2.5 grams of psyllium hemicellulose powder in 8 ounces of water taken three times per day. This will result in an intake of psyllium hemicellulose of 7.5 g/day. The product will also be labeled that it is not intended or recommended for use by children under 6 without a physician's guidance.

"Directions: One heaping TEASPOON in 8 ounces of water up to three times daily. Under 6 years: Consult a doctor. NOTICE: Mix this product with at least 8 oz (a full glass) of water. Taking without enough liquid may cause choking. Do not take if you have difficulty swallowing."

Proposed Mechanism of Action

Psyllium hemicellulose is considered to confer its beneficial health effects upon laxation, stool-softening, cholesterol-lowering and post-prandial glycemic response through its water-holding, polymer swelling, and gel-forming capability. It is proposed that the psyllium hemicellulose

polysaccharide binds water, thus increasing the stool mass, volume and lubricity, inducing peristalsis and thereby facilitating passage of the stool. It's hypothesized that psyllium hemicellulose's cholesterol lowering effect occurs because the increased viscosity of the aqueous layer at the intestinal lumen prevents bile acids from being reabsorbed so that they are lost through the stool. Blood cholesterol is lowered because cholesterol is being used to synthesize bile acids to replace those lost. An increase in viscosity of the fluids at the boundary of the intestinal lumen also delays absorption of sugars, thereby attenuating glycemic response.

V. Safety Assessment of Proposed Use of Psyllium Hemicellulose as a Dietary Supplement

As noted in the cover letter, the proposed use of psyllium hemicellulose as a dietary supplement is supported by an excellent safety record spanning over 70 years for psyllium, of which psyllium hemicellulose is an integral component.

History of Use

Psyllium has a long history of use throughout the world. Psyllium has been used in traditional medicine in India and finds mention in ancient Indian Ayurvedic prescriptions. It has also been used in traditional medicine in the US, Europe, and China. Some of the uses of psyllium in traditional medicine are as laxative, emollient, demulcent, and diuretic.

As a component of psyllium husk, the active ingredient in Metamucil®, psyllium hemicellulose (which makes up approximately 75% of psyllium) also has a long history of use in traditional and herbal medicine. The brand Metamucil®, containing psyllium, was introduced into the market in the United States over 70 years ago and has been on the market for several decades in Europe and Canada, and continues to be marketed as an over-the-counter bulk fiber laxative. Psyllium has an excellent safety record which has been further documented by other scientific groups including the Select Committee on Generally Recognized Safe Substances (1982), and the Expert Panel from the Life Sciences Research Office of the Federation of American Societies for Experimental Biology (1993).

Psyllium husk is derived from the seed of the *Plantago ovata* plant. Besides *Plantago ovata*, psyllium is also known as Ispaghula and Isapgol. *Plantago ovata* is an annual herb native to Asia, the Mediterranean region, and North Africa. Psyllium grows in sandy and silty soils.

Currently, psyllium is extensively cultivated in India and Pakistan. India provides about 85 percent of the psyllium available in the world market. The US is the world's largest importer of psyllium husk.

Currently in the US, psyllium husk is most often used as a bulk-fiber laxative, in foods or in various fiber supplements. In 1998, the Food and Drug Administration (FDA) authorized the use of a health claim in the labeling of foods and dietary supplements containing psyllium husk. The health claim for Metamucil® states that diets low in saturated fat and cholesterol that include 7 grams of soluble fiber per day from psyllium husk, as in Metamucil®, may reduce the risk of heart disease by lowering cholesterol. One adult dose of Metamucil® powder has 2.4 grams of this soluble fiber.

Clearly, there is a long-term history of exposure to psyllium hemicellulose in the form of consumption of psyllium-based products. Psyllium hemicellulose is a more concentrated form of the soluble hemicellulose naturally present in psyllium husk and its improved physical and chemical properties reflect the removal of the insoluble cellulose, lipids, proteins and psyllium seed components.

Toxicology Studies

The Select Committee on Generally Recognized as Safe Substances (SCOGS) of the Life Sciences Research Office of the Federation of American Societies for Experimental Biology evaluated the health aspects of psyllium seed husk gum as part of Contract No. FDA 223-78-2100 (1982). In addition, The Procter & Gamble Company has conducted several safety assessment studies on psyllium. Although these studies have not been published, they were conducted under GLP conditions and are valuable in the evaluation of psyllium safety. Thus, they are provided to further support the safety of psyllium hemicellulose which, as noted above, is an integral component of psyllium seed husk. These materials are COMPANY CONFIDENTIAL and are not to be released to any other entity, person or company without the written permission of The Procter & Gamble Company. Their presentation here provides further demonstrable support for the safety of psyllium hemicellulose as shown in well designed and conducted safety assessments. Thus, the P&G work as well as the studies cited in the SCOGS report are cited here as pertinent safety information.

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Effect of Dietary Psyllium on Mineral Balance

P&G conducted a 93-day study in 8 week old male Fischer 344 rats to assess the effect of psyllium on mineral balance (HPCR0322; Wood and Stoll, 1990). Animals were either fed a fiber free diet or a diet with psyllium at levels of 0, 1.0, 2.5, 3.75 or 5% (w/w) with cellulose added to yield a total dietary fiber level of 5.0%. Diets contained either 0.25% calcium or 0.5% calcium. The effect of these dietary fibers on the absorption of minerals (Ca, P, Mg, Fe, Cu, Mn, Zn, Na and K) was investigated. Fecal and urinary mineral excretion were measured at Days 30 and 86 and normalized for intake. Serum and bone mineral concentrations were determined after 93 days. When viewed collectively, the data indicate that the supplementation of diets with cellulose or psyllium had no adverse effects on the mineral excretion or status.

Effects of Psyllium on Blood Pressure

The cardiocirculatory effects of psyllium seed husk were evaluated by Fraschini (1978). Male Sprague-Dawley rats with in-dwelling blood pressure catheters in the abdominal aorta via the femoral artery were administered Metamucil® powder (500 mg/kg/day) or Metamucil® Instant Mix (500 mg/kg/day) for six days /week for a period of 20 days. Arterial pressures and cardiac rates were unchanged due to treatments.

Reproduction and Teratogenicity

The SCOGS report reported that psyllium formulations in aqueous suspension were administered by gastric intubation at doses of 0.5 and 1.0 g/kg body weight to 10 gravid Sprague-Dawley rats and 10 gravid New Zealand white rabbits on days 6 to 15 and 6 to 18 after conception respectively. Dosages of the "powder" formulation were 0.5 and 1.0 g/kg body weight and 0.5 g/kg body weight for the "instant dose" formulation. Necropsy of the rats on day 20 and the rabbits on day 30 of gestation revealed no significant differences between treated and control groups in the number of implantations or resorptions, or in number and weight of live fetuses. There were no dead or underdeveloped fetuses in the treated animals and no external, internal, or skeletal malformations found in the live fetuses. Another study of psyllium seed husk gum (*P.ovata*) in rabbits was conducted by Mercatelli and associates (1978). Psyllium seed husk gum was administered by oral intubation 200 or 400 mg/kg of body weight/day as a mixture of of the gum suspended in 1/3 v/v water: polyethylene glycol 400). Test compound was administered

from the 6th to 18th days of gestation; no deleterious effects were reported (Mercatelli et al., 1978).

In addition, P&G also conducted both a two generation reproductive and teratology study in rats (Sutton, 1993; HPCR 0397) and a teratology study in rabbits (Wood, 1994; HPCR 0605) at Hazelton Laboratories, North America.

In the first study, male and female Crl:CD®BR VAF/Plus® rats nine weeks of age (30/sex/group) were fed diets containing 0 (basal diet), 0 supplemented with 5% avicel, or 1, 2.5, and 5 % psyllium for 10 weeks throughout the F_0 and F_1 generations to assess the effect of psyllium on male and female mating performance and fertility; on the growth and development of the offspring from two consecutive generations; on gestation, parturition, and lactation; and on fetal development and teratogenesis. Clinical observations, body weights, food and water consumption, and reproduction and litter data were recorded for the F_0 and F_1 generations. In addition, cesarean section data and fetal external, soft tissue, and skeletal examinations were done for the F_{2b} litters.

The only psyllium-related clinical observation during the F_0 and F_1 generations were non-formed feces. The mean body weights for males in the F_0 and F_1 generations consuming 5% psyllium were generally lower than those of the control groups throughout premating. Mean body weights for the F_0 and F_1 5% psyllium-fed females were significantly higher than those of the control groups on Day 21 of lactation. With 2.5% dietary psyllium, the mean body weights for the males were generally lower than the basal diet controls throughout the F_1 generation. These differences were considered to be related to the dietary psyllium.

In the F_0 and F1 generations, mean cumulative body weight changes for the 5% psyllium-fed males were significantly lower than those of the control groups. Mean body weight gains for the 5% psyllium-fed F_0 and F_1 generation females were higher than those of the control groups during lactation. The differences in mean body weight changes were considered to be due to the dietary psyllium.

In the F_0 and F_1 generations, the significant differences in food consumption during premating and postmating for the males, and during premating for the females were sporadic and not related to consumption of psyllium. During gestation, food consumption was generally higher for the 1%, 2.5%, and 5% psyllium-fed F_0 and F_1 females than for the control groups. The increase in food consumption during gestation can be attributed to the ingestion of psyllium.

Water consumption was increased for the 2.5% and 5% psyllium-fed F_0 males compared to the control groups throughout premating. Significant differences in water consumption during premating for the F_0 females were sporadic. In the F_1 generation, the water consumption for the 5% psyllium-fed females was generally increased during premating. During gestation and lactation, water consumption for the F_0 and F_1 females was generally higher than that of the control groups.

During lactation for both generations, the mean water consumption for the 2.5% and 5% psyllium-fed females was significantly higher than that of the control groups. The increases in water consumption for the 2.5% and 5% males and females were considered to be related to the dietary psyllium.

There were no psyllium-related effects on reproductive performance, including mating performance and fertility. There were no significant differences in the sperm evaluation parameters. Pup weights were significantly reduced for the 2.5% and 5% psyllium-fed groups in both generations. There were no psyllium-related effects on fetal development.

In the F_0 and F_1 generations, terminal body weights were significantly lower in males given 5% dietary psyllium compared with males given the basal diet. No toxicologically important changes in absolute organ weights, organ-to-body weight percentages, or organ-to-brain weight ratios were observed. There were no psyllium-related macroscopic or histomorphologic changes in the F_0 or F_1 generations.

It can be concluded that when psyllium was administered to Crl:CD®BR rats continuously in the diet through two generations at concentrations as high as 5%, the no-observable-adverse effect levels were 5% for mating performance and fertility, 1% for offspring growth and development

(based on reductions in pup weights at 2.5% and 5%), and 5% for fetal development and teratogenesis.

The second study conducted by P&G (Wood, 1994; HPCR 0605) was a developmental toxicity study including assessing the teratogenic potential of psyllium when fed to pregnant rabbits before implantation and during organogenesis. Mated Hra: (NZW) SPF rabbits were received on either Day 2, 3, or 4 of Gestation and assigned at random to five groups of 20 animals each. Four groups received a basal diet of Purina Certified Rabbit diet #5322 to which psyllium was added at levels of 0%, 2.5%, 5.0%, or 10%. Purina Certified High Fiber Rabbit Diet #5325, used as a second control diet, was fed to another group. Animals received their respective diets on a restricted ration basis on the first day of receipt, and *ad libitum* thereafter through Day 29 of Gestation. Clinical observations for mortality/morbidity were performed twice daily. Body weights were recorded on Gestation Days 0, 4, 7, 10, 13, 16, 20, 24, and 29. Food and water consumption were measured daily beginning on Gestation Day 4. Cesarean sections and necropsies were done on surviving animals on Gestation Day 29, and the fetuses were removed for external, visceral, and skeletal examinations.

The clinical observations that were related to ingestion of the psyllium were confined to fecal findings. Ingestion of the 10% psyllium-containing diet resulted in lower mean body weights and body weight gains (including body weights and net body weight changes corrected for uterine weights). Mean food consumption of the groups that ingested the psyllium-containing diets tended to be lower than that of both control groups during gestation, and were significantly lower for most intervals. Mean water consumption of the group consuming 10% dietary psyllium was significantly lower than that of the control groups throughout gestation.

The findings observed at necropsy among animals that received the dietary psyllium were not considered to be related to treatment because of their low incidence.

Mean corpora lutea, implantation sites, total resorptions, and live fetuses of the groups that received the test materials were comparable to those of the control groups. There were no treatment related differences in the fetal sex ratios or mean fetal body weights of the psyllium-treated groups. There were no abnormal fetal morphological findings that were considered related to psyllium treatment. Fetal malformations and variations seen in the groups exposed to

psyllium throughout gestation were either low in incidence or were comparable with the findings seen in the control groups.

It can be concluded from this study that the no-observable-adverse-effect level for developmental toxicity is 10.0% based on the lack of adverse fetal findings. However, ingestion of psyllium resulted in lower maternal body weights, lower body weight gains, and water consumption at the 10.0% level, and abnormal fecal findings and lower food consumption at all dietary levels of psyllium tested.

Mutagenicity and Carcinogenicity

While no information is available on mutagenicity or carcinogenicity testing of psyllium, there are a number of core studies that support its lack of carcinogenicity. There was no evidence of carcinogenicity seen in five carcinogenesis bioassays conducted by the National Toxicology Program in 1982 on related GRAS fibers (locust bean gum, tara gum, guar, carrageenan, and gum arabic). When comparing psyllium to related GRAS fibers, similar physiological actions are seen (e.g., guar and cholesterol lowering, laxation, modulation of glucose absorption). There is general recognition of the safety of related food fibers (guar, carrageenan) for food use. Psyllium also has general recognition of safety by the medical and scientific community.

Comparisons between psyllium and guar in the P&G 91-day study referenced above demonstrated similar physiological effects (GI morphology by light microscopy, intestinal weight increases, food and water consumption, body weight gain, etc.). Psyllium and guar also produced similar intestinal effects based on results from a P&G 28-day morphometrics study. The six-month dog study identified in the SCOGS report above, as well as the 25-week rat study, and the P&G 91-day subchronic toxicity study all indicate no significant toxicity or lesions seen.

Finally, the history of extensive human exposure to psyllium-containing drugs (over 70 years of use in the U.S.) and monitoring of drug adverse reactions has revealed no unforeseeable chronic toxicity or carcinogenicity concerns.

All of the information cited above provides support for the safety of psyllium hemicellulose as an integral component of psyllium.

Summary of Animal Toxicology

Since psyllium hemicellulose comprises 75% of psyllium husk, it is clear that there is a reasonable expectation of a good margin of safety. The lack of any toxicological findings from any study on psyllium husk and, by extension, its major component psyllium hemicellulose, is supportive of a reasonable expectation of safety from its recommended use. Psyllium husk is practically non-toxic in acute animal studies at a dose up to 6 grams/kg of body weight. There were no maternal, embryotoxic or teratogenic effects in a teratology study in rats or rabbits given up to 500 mg/kg psyllium over most of the gestational period. In several early subchronic feeding studies in rats and in a limited number of dogs, psyllium husk did not produce any adverse toxicological effects. These studies clearly constitute a sufficient database to evaluate the potential toxicity of psyllium hemicellulose generally and as present in psyllium husk.

VI. Efficacy Studies in Animal Models

The details of the efficacy data and comparative animal studies on psyllium hemicellulose conducted by The Procter & Gamble Company (both internally and externally) are unpublished. These are provided as comparative data (between psyllium and psyllium hemicellulose). These materials are COMPANY CONFIDENTIAL and are not to be released to any other entity, person or company without the written permission of The Procter and Gamble Company. They deal with proprietary technology that is confidential and is not related to safety. Their presentation here is to provide further demonstrative support for the efficacy of psyllium hemicellulose in stool softening, laxation and cholesterol lowering in experimental animal models. The efficacy data support the fact that psyllium hemicellulose is the active component of psyllium seed husk. See summarized data in appendix A.

VII. Human Studies

Psyllium has been extensively studied as a "non-systemic" cholesterol lowering agent, in the treatment of constipation, fecal incontinence, hemorrhoids, ulcerative colitis, in appetite suppression, as an antidiarrheal agent and in Type 2 Diabetics. A Monograph on *Plantago ovata* and its effects in various clinical studies was prepared in 2002 (Alternative Medicine Review). The efficacy data support the fact that psyllium hemicellulose is comparable to psyllium seed husk. See summarized data in appendix B.

VIII. Consumer Research Tests on Psyllium Hemicellulose and Related Safety Information

An extensive number of psyllium hemicellulose product research tests have been conducted both in-house at P & G as well as with consumers. These data are presented in the Table below. The product is coded with the name Marlett and covers a period of four years worth of evaluations. It was tested in over 2400 subjects during this time period.

It is very important to note that the safety of psyllium hemicellulose has been reaffirmed here, with no significant or serious adverse events during these tests. Psyllium hemicellulose's low order of toxicity is very similar to that in the plethora of published work on psyllium husk.

Employee* and Consumer usage of Marlett (Psyllium Hemicellulose) in PRT (Product Research Test) studies - (Dec 2000 – Dec 2004)

All research was carried out in the United States, under carefully administered informed consents and confidentiality documents

Study name	Respondents	No. of respondents	Marlett Usage
EAS1	Employees	100	1 full single dose* once daily for 3 days
EAS2	Employees	100	1 full single dose once daily for 3 days
EAS3	Employees	100	No Marlett -Control
EAS4	Employees	100	1 full single dose once daily for 3 days
EAS5	Employees	100	5 full doses (1 a day for 5 days)
EAS6	Employees	100	1 full single dose once daily for 3 days
EAS7	Employees	100	No Marlett -Control

EAS8	Employees	120	1/3 of a single dose once only
EAS9	Employees	100	5 full doses (1 a day for 5 days)
Concept Fit (Baltimore)	Consumers	20	Up to 3 x daily usage for up to 14 days
In Touch (Atlanta)**	Consumers	40	Up to 3 x daily usage for up to 14 days
		24	1 partial dose only
Naming Study (multi site US)	Consumers	400	1 full single dose
In Touch Phoenix	Consumers	32	Up to 3 x daily usage for up to 14 days
Single Product Blind test	Consumers	650	Up to 3 x daily for up to 14 days
Bases	Consumers	380	Up to 3 x daily for up to 14 days

*Full single dose = 2.5 g/psyllium hemicellulose (Marlett)

**One transient and non-serious event was experienced in the "In-Touch" study; a female experienced itching of her skin and discontinued ingestion. The itching then resolved. No other unexpected or serious events were observed for the Marlett product in any of the other exposures.

Psyllium Hemicellulose Listing in Over-the-Counter (OTC) Monograph for Human Use

Psyllium hemicellulose is an approved active ingredient in the Laxative Drug Products for Over-the-Counter Human Use Tentative Final Monograph (FR 50, #10, Jan. 15, 1985; FR 51, #190, Oct. 1, 1986). The recommended oral dosage for adults and children 12 years of age and over is up to 30 grams daily in divided doses of 2.5 to 7.5 grams per dose. For children 6 years of age to under 12, dosage is up to 15 grams daily in divided doses of 2.5 to 3.75 grams per dose. Based on the fact that psyllium hemicellulose is listed as an FDA approved active ingredient in the laxative tentative final monograph, the agency agrees that this ingredient is safe for oral ingestion in OTC drug use.

Exposure Estimates for Psyllium Seed Husk in Food as It Relates to Psyllium Hemicellulose

The Federation of American Societies for Experimental Biology (FASEB) Life Science Research Office (LSRO) Expert Panel in 1993 established that consumption of one food item containing psyllium seed husk on a single serving occasion would result in mean intakes ranging from 1.9 to 5.3 grams per eating occasion for 1- to 2-year-old children and 4 to 12.1 grams for 15- to 18–year-old males. For the 90th percentile consumers, intakes would range from 3.8 to 11.0 grams per eating occasion for 1- to 2-year-olds and from 7.5 to 21.9 grams per eating occasion for 15- to 18-year-old males.

Further, on the basis of usual consumption, consumption of one item containing psyllium seed husk would result in mean intakes of 0.7 to 2.7 grams/day for 1- to 2-year-old children and 1.3 to 5.4 grams/day for 15- to 18-year old males. For the 90th percentile consumers, psyllium seed husk intake from one food item would range from 1.3 to 5.7 grams/day for 1-to 2-year old children and 2.7 to 11.3 grams/day for adolescent males. These consumption projection estimates raised no safety concerns by the Expert Panel who noted that while total dietary fiber intake would not increase appreciably, it is reasonable to expect that persons preferentially consuming products containing psyllium seed husk might ingest 25 grams/day of psyllium seed husk. This level would equate to consumption of 18.75 grams of psyllium hemicellulose from the psyllium seed husk.

Side Effects/Toxicity

No adverse effects of clinical significance from consuming psyllium seed or husk have been reported in clinical studies. There were also no changes reported in vitamin or mineral content in any of the studies referenced above. A 52-week study by Oliver, (2000) of 93 healthy individuals did find there were some small but statistically significant changes in some measurements of mineral and vitamin levels and in some hematological and biochemical parameters. None of these were of clinical significance with the possible exception of insignificant changes in vitamin B_{12} levels. As noted by the Expert FASEB Panel in 1993, there are no anecdotal or clinical observations of possible effects on vitamin or mineral absorption or metabolism from a long history of use of psyllium–containing laxatives.

Adverse Effects/Contraindications

Several cases of allergy, hypersensitivity, anaphylaxis, choking due to esophageal blockage from granular forms, and asthma have been reported in the literature related to psyllium so caution must be exercised in allergy-prone individuals and those with difficulty swallowing. The majority of the allergic responses were due to occupational exposure and continuous handling. Khalili et al., (2003) provide a recent case report and review of the literature.

IX. Claims

A product (Marlett) containing psyllium hemicellulose will be marketed as a fiber supplement, utilizing wording such as "an easy way to increase your daily fiber." It is the intent of The Procter & Gamble Company to market this product with claims indicating that it promotes regularity and active GI function. Psyllium hemicellulose is a bulk-forming fiber derived from psyllium husk. Other bulk-forming fibers include cellulose, methylcellulose, sodium carboxymethylcellulose, karaya, malt soup extract, polycarbophil, and wheat bran. Bulk-forming fibers have laxative effects because of their water-holding properties. They exert their action primarily through mechanical effects by bulking the colonic contents and shortening transit time.

It is well known that fiber helps to maintain normal bowel function, to prevent constipation and its potential complications. Straining and pressure from constipation may lead to diverticular disease and hemorrhoids. There is also increasing evidence that a diet high in fiber and low in fat may help in the prevention, management, or treatment of certain conditions. It is also well known that Americans consume only about half the fiber they need each day from their diet. Psyllium hemicellulose contains a high level of soluble fiber that is safe and can assist in providing and maintaining normal bowel function.

X. Safety Assessment Summary

The safety of psyllium hemicellulose has been well established in a fairly comprehensive set of animal studies (Appendix A) in addition to the large database of safety studies on psyllium discussed previously. No evidence for acute toxicity or adverse effects were found, and in subchronic feeding studies in rats and dogs, doses exceeding 500 mg/kg body weight/day of psyllium husk of which 75% is psyllium hemicellulose have not resulted in toxicological effects.

In addition, teratology studies with up to 10% psyllium seed husk powder were not associated with any treatment related developmental or teratogenic effects in rats or rabbits.

A history of use that spans more than 70 years for psyllium seed husk as well as many clinical trials in humans, with dosing durations up to 52 weeks at intakes up to 10.5 grams of psyllium per day, have not produced any adverse effects, with the possible exception of an insignificant effect on vitamin B_{12}. No such effect was observed at up to 20.4 g/day over a period ranging from 6 weeks to 6 months where psyllium was well tolerated. The exposed population included subset groups of the elderly (>65 years), subjects with Type 2 diabetes, and obese subjects. Although rare, allergic reactions to psyllium including topical dermatitis, asthma and, on rare occasions, anaphylaxis have been reported, generally in individuals with prior psyllium exposure from either manufacturing or bulk dispensing. Psyllium labeling provides information about this issue: "This product may cause allergic reaction in people sensitive to inhaled or ingested psyllium". Similar labeling would be used for psyllium hemicellulose.

Since psyllium hemicellulose comprises 75% of psyllium husk powder, a 10.5 gram dose of psyllium seed husk provides the equivalent of 7.88 grams of psyllium hemicellulose or 131 mg/kg of body weight/day for a 60 kg individual. All of the safety data reviewed in this assessment support the conclusion that an intake of psyllium hemicellulose at 2.5-7.5 grams/day (125 mg/kg/day) poses no safety concerns. The OTC laxative monograph supports dosing of 30 grams per day.

We think that the composition data and toxicology database is reasonably complete to support this comparison of psyllium husk and psyllium hemicellulose. Further, the Select Committee on GRAS Substances (1982) concluded that 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. The US FDA (1998) further affirmed this conclusion with their allowance of a health claim for soluble fiber from psyllium seed husk and a decreased risk of coronary heart disease. The Expert Panel of the Life Sciences Research Office (1993) also evaluated the safety of using psyllium seed husk as a food ingredient and concluded that it is safe for the intended uses. This Expert Panel stated that there is no evidence in the available information on psyllium

husk 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 grams/day of psyllium seed husk. By extension, as the integral component of psyllium seed husk (75%), we conclude that the evidence cited above is clearly supportive of the same safety conclusion for psyllium hemicellulose as a dietary supplement at the levels proposed.

XI. References

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