Appendix B: Human Studies

Constipation and Laxation

Many studies have shown that dietary fiber shortens gastrointestinal transit time and increases stool weight. The American Dietetic Association in 2002 issued a Position Statement on the Health Implications of Dietary Fiber. In this statement they indicated that the public should consume adequate amounts of dietary fiber from a variety of plant foods with recommended intakes of 20-35 grams/day for healthy adults and 5 grams/day plus for children. They noted that these levels were not being met because of low intakes of good sources of dietary fiber. Further, it is noted in this position statement that when food intake is low, as is the case among inactive elderly for both, a supplement may be needed to bring fiber intakes into a range adequate to prevent constipation.

When 18 grams psyllium husk was given to healthy volunteers, fecal weight and the production of short chain fatty acids were increased (Marteau et al., 1994). Most of the psyllium was shown to reach the cecum four hours after ingestion in an intact and highly polymerized form. The husk appears to be relatively resistant to fermentation. Marlett et al., (2000) also showed that the unfermented gel component of psyllium seed husk promotes laxation in humans by acting as a lubricant, increasing the level of stool moisture, as well as wet and dry stool weight. Marlett and Fischer (2003) conducted a series of experiments and evaluations of fractions isolated from psyllium seed husk to test the overall hypothesis that a gel-forming component of psyllium seed husk is not fermented and that it is this component that is responsible for the laxative and cholesterol-lowering properties of psyllium seed husk. A gel was isolated from human stools collected during a controlled diet study when psyllium seed husk was consumed. Evaluations of three fractions isolated from psyllium seed husk suggest that gel-forming Fraction B, which is about 75% of psyllium seed husk, is poorly fermented and is the component that increases stool moisture and fecal bile acid excretion, the latter leading to lower blood cholesterol levels. The active fraction of psyllium seed husk is a highly-branched arabinoxylan consisting of a xylose backbone and arabinose- and xylose-containing side chains. In contrast to arabinoxylans in cereal grains that are extensively

fermented, psyllium seed husk possesses a structural feature that hinders its fermentation by typical colonic microflora. Fischer et al., (2004) characterized the physiologically active, gel-forming fraction of the alkali-extractable polysaccharides of *Plantago ovata Forsk* seed husk (psyllium seed husk) by compositional and methylation analysis and NMR spectroscopy. Resolving the conflicting claims of previous investigators, the material was found to be a neutral arabinoxylan (arabinose 22.6%, xylose 74.6%, molar basis; only traces of other sugars). With about 35% of nonreducing terminal residues, the polysaccharide is highly branched. The data are compatible with a structure consisting of a densely substituted main chain of beta-(1-->4)-linked d-xylopyranosyl residues, some carrying single xylopyranosyl side chains at position 2, others bearing, at position 3, trisaccharide branches having the sequence l-Araf-alpha-(1-->3)-d-Xylp-beta-(1-->3)-l-Araf. The presence of this sequence is supported by methylation and NMR data, and by the isolation of the disaccharide 3-O-beta-d-xylopyranosyl-l-arabinose as a product of partial acid hydrolysis of the polysaccharide.

Voderholzer et al., (1997) reported a clinical study on the effectiveness of psyllium in a study of 149 patients with chronic constipation. They found that consumption of 15-30 grams daily of a psyllium seed preparation provided bowel relief in 85% of the subjects who had no known pathological cause for their constipation. Only 20% of individuals with slow transit responded to psyllium, but a greater percentage (37%) of those with disorders of defecation-including rectocele, internal prolapse, animus, and rectal hyposensitivity found improvement.

Dettmar and Sykes (1998) conducted an open, multi-centre study in general practice comparing efficacy, speed of action and acceptability of ispaghula husk (Fybogel Orange, Reckitt & Colman Products, UK), lactulose and other laxatives in the treatment of patients with simple constipation. A total of 65 physicians recruited 394 patients, of whom 224 (56.9%) were assigned to treatment with ispaghula and 170 (43.1%) to other laxatives (mainly lactulose) for up to four weeks. Thirteen patients withdrew before treatment started, so that 381 entered the study. Patients were assessed by their physicians before entry and after two and four weeks of treatment. Patients also kept daily records of

their bowel movements. After four weeks' treatment, ispaghula husk was assessed by the physicians to be superior to the other treatments in improving bowel function and in overall effectiveness, palatability and acceptability. Patients' reports of time to first bowel movement showed little difference between the treatments. Over 60% of patients in each treatment group passed a first motion within 24 hours, and over 80% within 36 hours. Ispaghula husk produced a higher percentage of normal, well-formed stools and fewer hard stools than other laxatives. Incidences of soiling, diarrhea and abdominal pain were lower in the group receiving ispaghula husk. Overall, ispaghula husk was an effective treatment for simple constipation, and was associated with better stool consistency and a lower incidence of adverse events compared with lactulose or other laxatives.

Fecal Incontinence

Because of psyllium's ability to retain water, it has also been shown by Bliss et al., (2001) to benefit individuals with fecal incontinence from liquid stools or diarrhea. A placebo-controlled trial of individuals with liquid stool fecal incontinence was performed with psyllium supplementation; it showed approximately a 50-percent decrease in the occurrence of incontinent stools.

Hyperlipimic and Hypocholesterolemic Effects

Psyllium husk has been shown to be an effective adjunct to dietary intervention for individuals who do not adequately respond to a low-fat, low-cholesterol diet (Anderson et al., 1991). Sprecher et al., (1993) demonstrated a 3.5% reduction in total cholesterol and a 5.1% reduction in LDL levels after consuming 5.1 grams of psyllium husk twice daily for eight weeks. Bell et al., (1989) showed that giving psyllium for eight weeks to individuals who were on the American Heart Association Step-1 diet resulted in decreased total cholesterol (4.8%) and LDL (8.8%). Anderson et al., (2000) performed a Meta analysis on eight trials of psyllium husk in conjunction with a low-fat diet in the treatment of hypercholesterolemia. After an initial eight-week, low-fat diet run-in, 10.2 grams psyllium were given per day for $\geq$ 8 weeks, resulting in a 4 % reduction in total cholesterol and 7% in LDL cholesterol, compared to diet and placebo. They also reported a 6% reduction in the ratio of apolipoprotein (apo) B to apo-A-1. Longer trials

[16 weeks (Levin et al., 1989) and 26 weeks (Anderson et al., 2000)] further confirmed these results.

The hypocholesterolemic effects of psyllium-enriched ready-to-eat cereals have also been reported by Anderson et al., (1992) and Jenkins et al., (1997). In addition, Olson et al., (1997) conducted a meta-analysis of 12 studies (8 published, 4 unpublished) of psyllium-enhanced cereals (3-12 grams psyllium/day) in hypercholesterolemic individuals already consuming a low-fat diet. Results mirrored the earlier meta-analysis in that serum cholesterol concentrations were reduced an additional 5 %, and serum LDL-cholesterol concentrations an additional 9% relative to placebo, in addition to reduction achieved via diet. Davidson et al., (1998) also reported, in a 24-week study of subjects consuming 3.4, 6.8, or 10.2 grams psyllium daily as a part of an AHA Step-1 diet, a 5.3% LDL-cholesterol reduction with 10.2 g psyllium/day. Romero et al., (1998) demonstrated that fiber-enhanced cookies fed for eight-weeks to a population of hypercholesterolemic men, using wheat bran-, psyllium-, or oat bran-containing cookies, resulted in a 22.6% reduction of LDL-cholesterol with psyllium and a 26% reduction in the oat bran group.

In studies of elderly patients by Burton et al., (1982) of 4 months duration at a dose of between 25-30 grams/day and by Stewart et al., (1991) where psyllium was consumed for one year, reductions were also noted for serum cholesterol as well as stool softening. The latter authors found that for every one-gram increase in daily psyllium dose there was a 0.022 mmol/liter (0.84 mg/dl) decrease in serum total cholesterol concentration.

Vega-Lopez et al., (2001) examined the effect of psyllium on blood lipids as it relates to age and gender differences in men and pre- and postmenopausal women who were given 15 grams of psyllium daily for 30 days. Psyllium lowered plasma LDL cholesterol by 7-9% in all groups. Triglycerides were lowered by 17% in men, but were increased by 16% in postmenopausal women whereas no effect was seen in premenopausal women. In a follow-up study reported in 2002, Vega-Lopez et al. further explored the mechanisms by which sex and hormonal status influence the effects of psyllium on plasma lipids. HMG-CoA reductase, LDL receptor and lipoprotein lipase (LPL) mRNA abundance were

measured in mononuclear cells isolated from these subjects. The intervention followed a randomized crossover design in which participants were allocated to either 15 or 0 g (control) of psyllium/d for 30 days. Compared to the control period, psyllium intake induced a 20% increase in HMG-CoA reductase mRNA abundance while no significant changes in LDL receptor mRNA abundance were observed. In contrast, LPL mRNA abundance was 24% higher in men and 23% lower in postmenopausal women when comparing psyllium intake with the control period. These results suggest that the LDL-C lowering induced by psyllium was related to changes in HMG-CoA reductase gene expression in monocytes while the expression of LPL in this system was affected by sex and hormonal status.

In 1998 the US Food and Drug Administration further affirmed its safe use by allowing a health claim for soluble fiber from certain foods including psyllium seed husk.