Bureau Nieuwe Voedingsmiddelen
Novel Foods Unit

Psyllium Zaadhuid *(Plantago ovata)*

Psyllium Seed Husk *(Plantago ovata)*

Tweede beoordeling van de veiligheid voor de consument, volgens de Europese verordening 258/97 betreffende nieuwe voedingsmiddelen en nieuwe voedselingrediënten

Second opinion regarding consumer safety, in accordance with European Regulation 258/97 concerning novel foods and novel food ingredients

aan/to:

de Minister van Volksgezondheid, Welzijn en Sport
the Minister of Health, Welfare and Sport

Nr. 2008-03 BNV, Den Haag, 4 augustus 2008
No. 2008-03 BNV, The Hague, August 4, 2008

Bureau Nieuwe Voedingsmiddelen
CBG
Postbus 16229
2500 BE Den Haag
novelfoods@cbg-meb.nl
www.nieuwevoedingsmiddelen.nl

Novel Foods Unit
MEB
P.O. box 16229
2500 BE The Hague
The Netherlands
novelfoods@cbg-meb.nl
www.novel-foods.nl

Inhoudsopgave

Contents

Beoordeling

Inleiding

Aan de orde is een tweede beoordeling volgens de Europese Verordening 258/97, over het gebruik als nieuw voedselingrediënt van Psyllium Seed Husk (PSH).

De aanvraag is ingediend door Kellogg Compagny, uit Ierland. Het product uit deze aanvraag, dat wordt aangeduid als PSH, wordt via een eenvoudig bewerkingsproces geproduceerd uit de zaadhuid van de *Plantago ovata* Forssk. (*P. ispaghula* Roxb.), ook psyllium, ispaghula of vlozaad genoemd. Deze plant komt van nature voor in Zuid-Europa, Rusland en Azië en wordt al jarenlang geteeld in Zuid-Europa, India en de VS voor gebruik in laxeermiddelen.

Het is de bedoeling van de fabrikant het nieuwe product als ingrediënt toe te voegen aan ontbijtgranen en granenrepen. In de EU werd PSH niet toegepast in gewone voedingsmiddelen voor 15 mei 1997 en daarom is een veiligheidsbeoordeling als nieuw voedingsmiddel vereist. In het kader van de desbetreffende Europese toelatingsprocedure is deze tweede beoordeling uitgevoerd door het Bureau Nieuwe Voedingsmiddelen van het College ter Beoordeling van Geneesmiddelen. Het bureau heeft hiervoor de Commissie Veiligheidsbeoordeling Nieuwe Voedingsmiddelen geraadpleegd, hierna genoemd ‘de Commissie VNV’.

Eerste beoordeling

De eerste beoordeling van de aanvraag voor markttoelating is verricht in Ierland door de *Food Safety Authority of Ireland* (FSAI).

De FSAI concludeert dat geen significante gezondheidsrisico’s te verwachten zijn en heeft geen bezwaar tegen markttoelating uitsluitend voor gebruik in ontbijtgranen en granenrepen (3.5 g per portie), mits PSH wordt geproduceerd volgens voorgestelde procedure en voldoet aan de specificatie. De aanvrager vermeldt dat de kans dat allergische reacties optreden sterk is gereduceerd door technlogische aanpassingen in het productieproces (zuiverheid van 85% naar 95%). Toch is het volgens FSAI niet uit te sluiten dat PSH bij individuele consumenten een overgevoeligheidsreactie zou kunnen veroorzaken en wordt geadviseerd middels adequate etikettering dit aan de gebruiker te communiceren.

Bevindingen van de Commissie VNV en Conclusie

De Commissie VNV heeft haar oordeel gebaseerd op de informatie in het dossier (1), waarvan de samenvatting is opgenomen als bijlage A, de eerste beoordeling door de FSAI (2), toegevoegd als bijlage B, en andere bronnen (3,4,5).

De aanvrager noemt twee producten waarin de nieuwe ingrediënten zullen worden verwerkt, ontbijtgranen en graanrepen, die per portie ten hoogste ongeveer 3.5 g PSH zullen bevatten. Daarnaast vermeldt de aanvrager andere soorten (eind)producten als mogelijke toepassing, zoals gebak en biscuits, maar daarvan zijn geen innamegegevens opgenomen.

De Commissie VNV heeft geen bezwaar tegen de toelating van PSH in de EU en is het eens met de positieve beoordeling door de FSAI. De Ierse beoordeling stelde wel de voorwaarde om te waarschuwen voor overgevoeligheid voor dit product. De Commissie wijst erop dat de gevallen van overgevoeligheid betrekking hadden op een ruwer

psylliumpreparaat en niet op PSH. Zij vindt wel dat aandacht moet worden besteed aan dit punt. Of PSH als mogelijk allergeen op de verpakking moet worden vermeld, moet worden bezien in samenhang met de bepalingen van Richtlijn 2003/89/EC.

Ook de gegevens over psyllium als voedingssupplement en de ervaring met PSH-bevattende granenproducten in de VS, Canada en Australië onderbouwen de veiligheid. De Commissie verwacht geen nadelige gezondheidseffecten na consumptie van PSH in ontbijtgranen en granenrepen. Zij meent dat het gebruik net zo veilig is als dat van andere, aan voeding toegevoegde vezelproducten.

Wel wijst de Commissie erop dat in het dossier weinig aandacht wordt besteed aan eerdere meldingen van spijsverteringsklachten als gevolg van onvoldoende vochtinname bij een psyllium bevattend voedingssupplement. Aangezien het product uit deze aanvraag slechts voor 12% uit psylliumvezel bestaat en ontbijtgranen meestal met vocht worden ingenomen, wordt verondersteld dat bij de toepassing die in dit dossier wordt besproken, dit aspect van minder belang is.

Productieproces en productspecificatie

Het productieproces voor de bereiding van PSH uit psylliumzaden bestaat uit twee stappen. De oogst en eerste bewerking van de geteelde psylliumzaden vinden plaats in India. Daarbij wordt de zaadhuid (zemel) van het zaad gescheiden en vermalen. Vervolgens wordt het in de VS verder gezuiverd en bewerkt tot het uiteindelijke ingrediënt.

In het dossier worden resultaten van drie batches gepresenteerd en vergeleken met een beperkte productspecificatie (conform de Farmacopee van de VS (USP) 2006).

De Commissie VNV heeft hierover geen opmerkingen en vindt dat het product voldoende is gespecificeerd. Wel wordt door de Commissie VNV opgemerkt dat in het dossier niet overal de term PSH eenduidig gehanteerd wordt (namelijk ook voor tussenproducten).

Geschiedenis van het bronorganisme

In de gebieden van herkomst wordt psylliumzaad traditioneel medicinaal toegepast bij diverse aandoeningen van het spijsverteringssysteem. Psylliumzaad/vezel wordt in Europa al jarenlang verwerkt in medicijnen en voedingssupplementen, als middel bij darmklachten. Er is echter geen ervaring met deze vezel in gewone voedingsmiddelen.

De Commissie VNV heeft geen verdere vragen over de geschiedenis van gebruik.

Inname

Volgens het dossier zullen ontbijtgranen en granenrepen 3.5 g PSH per portie bevatten.
In Annex E van het dossier staan voedselconsumptiegegevens uit het Verenigd Koninkrijk, om een schatting te maken van de mogelijke inname van PSH bij voorgestelde toepassing. In absolute zin werd de maximale inname geschat op 14.7 g PSH per dag (97.5^{e} percentiel van jongens van 11 tot 18 jaar), wat overeen zou komen met 256 mg PSH per kg lichaamsgewicht. Bij jonge kinderen kan de inname per kg nog hoger uitkomen, nl. 328 mg PSH per kg lichaamsgewicht.

De Commissie VNV deelt de visie van de eerste beoordelaar dat deze beoordeling uitsluitend betrekking heeft op toepassing van PSH in ontbijtgranen en graanrepen. Zij is van mening dat de aanvrager een degelijke inschatting van de te verwachten inname heeft gemaakt.

Eerdere blootstelling

De eerste beoordelaar citeert uit een aanvullende referentie (US select Committee on GRAS Substances in 1982) dat een geschatte 4 miljoen mensen in de VS waren blootgesteld aan lage gehaltes van psylliumvezel gedurende 20 jaar zonder dat daaraan geassocieerde gezondheidsrisico's optraden. Dit document is echter niet opgenomen in het dossier.

Voor supplementen bedraagt de aanbevolen dagelijkse dosering van psylliumvezel 3.5-10 g gedurende een paar weken.

In de VS, Canada en Australië zijn overeenkomstige, met PSH verrijkte ontbijtgranen reeds tot de markt toegelaten; uit de resultaten van Post Marketing Studies uit VS en Canada (1999-2005) zijn geen ernstige gezondheidsrisico's naar voren gekomen.

Het oordeel van de Commissie is dat het dossier voldoende inzicht geeft in eerder gebruik van producten met psyllium.

Voedingskundige informatie

PSH zal gedeeltelijk andere voedingsvezels vervangen in de voeding en kan ook een aanvullende bron van vezels in het dieet zijn. Het voedingskundig profiel staat in het dossier uitgewerkt in tabel XI.1-1. Daaruit blijkt dat PSH voornamelijk bestaat uit koolhydraten (in de vorm van hemi-cellulose) en een laag totaal vet- en eiwitgehalte heeft (beide 2%). Het bevat geen verzadigd vet. Uit de tabel blijkt verder dat het product voor 83% als voedingsvezel kan worden gezien, waarvan het grootste deel gekarakteriseerd is als oplosbare vezel.

Het dossier vermeldt resultaten uit dier- en humane studies die aantonen dat door binding van psylliumvezel de absorptie in de darm van vitaminen en mineralen enigszins wordt verminderd. Deze reductie zou marginaal zijn en niet klinisch relevant.

De Commissie VNV vindt dat vanuit voedingskundig oogpunt PSH vergelijkbaar is met andere vezelproducten en voorziet geen specifieke problemen in het voedingskundige aspect.

Microbiële informatie

Microbiële analyses worden uitgevoerd na aankomst van het ruwe plantenmateriaal in de VS. De testen omvatten controle op aërobe bacteriën, gisten, schimmels, *E. coli*, *Salmonella*, *P. aeruginosa* en *S. aureus*. Volgens de eerste beoordelaar voldoen de getoonde resultaten van 3 batches aan de specificaties (conform USP 2006) en geven deze geen aanleiding te twijfelen aan de microbiële zuiverheid van het product .

De Commissie VNV deelt deze conclusie.

Toxicologische informatie

Het dossier gaat ervan uit dat PSH grotendeels onveranderd het lichaam verlaat. Volgens de aanvrager suggereren studieresultaten dat tot 6% van de ingenomen PSH in de maag wordt gehydrolyseerd onder afsplitsing van l-arabinose, dat normaal wordt opgenomen en gemetaboliseerd. Uit *in vitro* studies en dierproeven concludeert de aanvrager dat een klein deel wordt gefermenteerd. Voldoende resultaten uit humane studies ontbreken om hierover verdere uitspraken te doen.

Uit een reeks toxiciteitstudies is gebleken dat psyllium(vezel) een lage acute toxiciteit bezit en goed wordt verdragen. Studieresultaten uit subchronische studies toonden aan dat bij proefdieren pigmentatie kan optreden in de epitheelcellen van de verzamelbuisjes van de

nieren na inname van een psylliumproduct. Het dossier meldt dat deze verkleuring niet optreedt na toediening van via het nieuwe proces bereide product PSH.
Klinisch onderzoek toonde aan dat dagelijkse doses tot 30 g psyllium(vezel) goed worden verdragen. Als bijwerkingen werden genoemd: milde GI-symptomen als flatulentie, opgeblazen gevoel en diarree. Deze werden gerelateerd aan de hoge vezelinname en verdwenen na de behandeling weer. Een vergelijkbaar effect is waargenomen in humane studies na inname van andere vezels, o.a. tarwezemelen.

Er zijn geen studies beschikbaar met betrekking tot de reproductieve toxiciteit en genotoxiciteit.

Het dossier vermeldt een aantal publicaties met meldingen van spijsverteringsproblemen (o.a. slokdarmobstructies) na gebruik van een psylliumbevattend supplement; deze bijwerkingen konden worden verklaard door een gebrek aan voldoende inname van vocht en/of onjuist gebruik van het product.

De Commissie VNV heeft geen vragen over dit onderdeel van het dossier.

Allergeniteit

In eerdere publicaties over psyllium(vezel) is melding gemaakt van allergeniteit. Volgens het dossier was er sprake van sensibilisatie van mensen die beroepshalve al veel in aanraking waren gekomen met psyllium, zoals verpleegkundigen, apothekers en medewerkers bij farmaceutische bedrijven. Na inname van psyllium bevattende producten, o.a. ontbijtgranen, werden in enkele gevallen o.a. luchtwegklachten en in een zeldzaam geval anaphylaxis gerapporteerd. In de loop van de tijd is de aanvrager overgegaan op een productieproces waarbij een extra zuiveringsstap is toegevoegd aan het productieproces (van 85% naar 95% zuiverheid). Men vermoedde dat de allergene stof zich vooral in het zaad onder de zaadhuid bevindt. Tevens heeft het bedrijf besloten om bij producten buiten de EU via etikettering een waarschuwing op te nemen voor overgevoeligheid. Volgens de aanvrager is na het uitvoeren van deze maatregelen het aantal meldingen van allergie sterk afgenomen.

De Commissie VNV deelt de conclusie van de eerste beoordelaar dat aandacht besteed moet worden aan de allergeniteit. Of PSH als mogelijk allergeen op de verpakking moet worden vermeld, moet worden bezien in samenhang met de bepalingen van Richtlijn 2003/89/EC.

Referenties

1 'Application for the Approval of Psyllium Seed Husk (PSH)', product dossier van Kellog Compagny (2007)

2 'Initial Assessment Report of the Application for the Authorisation of Psyllium Seed Husk (PSH) from Plantago ovata under Article 4 of the Novel Food Regulation (EC) No. 256/97', Food Safety Authority of Ireland (april 2008).

Aanvullende bronnen:

3. 'Assessment report on *Plantago ovata* Forssk., seminis tegementum', EMEA/HMPC (2006)
4. 'Community monograph on *Plantago ovata* Forssk., semen', EMEA/HMPC(2006)
5. 'Voedingsvezel", Voedsel en Waren Autoriteit (2007), via http://www.vwa.nl

Assessment (English courtesy translation)

Introduction

The subject in question is a second assessment, in accordance with European Regulation 258/97, regarding the use of Psyllium Seed Husk (PSH) as a novel food ingredient.

The application was submitted by the Kellogg Company of Ireland. The product cited in this application, designated as PSH, is produced by means of a simple production process from the seed husk of *Plantago ovata* Forssk. (*P. ispaghula* Roxb.), also known as psyllium, ispaghula or fibre husk. This plant occurs naturally in southern Europe, Russia and Asia. For many years, it has been cultivated in southern Europe, India and the US, for use in laxatives.

The manufacturer intends to use the novel product as an ingredient of breakfast cereals and cereal bars. As PSH was not used in foods in the EU prior to 15 May 1997, a novel food safety assessment is required. In the framework of the relevant European approval procedure, this second assessment was prepared by the Novel Foods Unit of the Medicines Evaluation Board. To this end, the Unit consulted the Committee on the Safety Assessment of Novel Foods (hereafter referred to as 'the VNV Committee').

Initial assessment

The initial assessment of the application for market authorisation was carried out in Ireland, by the Food Safety Authority of Ireland (FSAI).

The FSAI concluded that no significant health risks are anticipated. Accordingly, it has no objection to market authorisation exclusively for use in breakfast cereals and cereal bars (3.5 g per portion). This is subject to the condition that PSH is produced in accordance with the proposed procedure and that it meets the specification. The applicant reports that, as a result of technological modifications to the production process (boosting purity from 85% to 95%), the risk of allergic reactions has been greatly reduced. Even so, according to the FSAI, the possibility of PSH causing an allergic reaction in individual consumers cannot be ruled out. Accordingly, it is recommended that adequate labelling be used to communicate this information to users.

Findings of the VNV Committee and Conclusion

The VNV Committee based its judgement on the information contained in the dossier (1), the summary of which is included as annex A, the FSAI's initial assessment (2) included as annex B, and other sources (3, 4, 5).

The applicant cites two products into which the novel ingredients will be incorporated: breakfast cereals and cereal bars. These will contain no more than approximately 3.5 g of PSH per portion. In addition, the applicant reports possible use in other types of products (and end-products), such as cakes and biscuits, but no intake data has been included.

The VNV Committee has no objection to the authorisation of PSH in the EU, and concurs with the favourable assessment by the FSAI. However, the Irish assessment does impose the condition that a warning be included regarding the allergenic potential of this product. The Committee points out that the cases of allergy related to a cruder psyllium preparation and not to PSH. The Committee nevertheless believes that consideration should be given to this point. The question of whether PSH should be listed on the packaging as a

possible allergen will have to be considered in conjunction with the provisions of European Directive 2003/89/EC.

Details concerning the use of psyllium as a food supplement and about the experience gained with PSH-containing cereal products in the US, Canada and Australia, also substantiate their safety. The Committee does not anticipate that the consumption of PSH in breakfast cereals and cereal bars will have any adverse effect on health. It takes the view that the use of PSH is just as safe as that of other fibre products that are added to food.

The Committee does point out, however, that the dossier pays little attention to earlier reports of gastrointestinal symptoms resulting from inadequate liquid intake when using a food supplement containing psyllium. As psyllium fibre makes up just 12% of the product in this application, and as breakfast cereals are usually consumed with liquid, it is assumed that, for the use outlined in this dossier, this aspect is of no major concern.

Production process and product specification

The preparation of PSH from psyllium seeds involves a two-step production process. The harvesting and initial processing of the cultivated psyllium seeds takes place in India. The seed husk (bran) is then separated from the seed and milled. It is then further purified in the US, where it is processed into the final form of the ingredient.

The results from three different batches are presented in the dossier, and are compared to a limited product specification (in accordance with the United States Pharmacopeia (USP) 2006).

The VNV Committee has no comments to make about this and is of the opinion that the product has been adequately specified. However, the VNV Committee notes that the dossier includes some ambiguous uses of the term PSH (i.e. it is also used for intermediate products).

History of the source organism

In its areas of origin, psyllium seed is traditionally used as a medication, to treat various disorders of the gastrointestinal system. In Europe, psyllium seed/fibre has been used for many years in medicines and food supplements, as a treatment for intestinal symptoms. However, this fibre has never previously been used here in normal foods.

The VNV Committee has no further questions about the history of use.

Intake

According to the dossier, breakfast cereals and cereal bars contain 3.5 g of PSH per portion. The potential intake of PSH in its proposed use has been estimated using food consumption data from the UK, which is provided in Annex E of the dossier. In absolute terms, the maximum intake was estimated to be 14.7 g PSH per day (the 97.5th percentile of boys aged 11 to 18), which would correspond to 256 mg PSH per kg body weight. In young children, the intake per kg can be even higher, i.e. 328 mg PSH per kg body weight.

The VNV Committee concurs with the view of the first assessor, that this assessment relates only to the use of PSH in breakfast cereals and cereal bars. The Committee is of the opinion that the applicant has made a reliable estimate of the anticipated intake.

Previous exposure

Citing from a supplementary reference (US Select Committee on GRAS Substances in 1982), the first assessor states that an estimated four million people in the US had been exposed to low levels of psyllium fibre for 20 years, yet there was no evidence of any associated health risks. However, the document in question is not included in the dossier.

For supplements, the recommended daily dose of psyllium fibre is 3.5 -10 g over the course of a few weeks.

Similar breakfast cereals fortified with PSH have already been introduced to the market in the USA, Canada and Australia. Post-marketing studies have been carried out in the USA and Canada (1999-2005), but no serious health risks have come to light.

The Committee takes the view that the dossier provides satisfactory insight into the previous uses of psyllium-containing products.

Nutritional information

PSH will partially replace other fibres in the diet, and can also be an additional source of fibre. Details of its nutritional profile are given in table XI.1-1 of the dossier. This shows that PSH principally consists of carbohydrates (in the form of hemicellulose) and that it has a low total fat and protein content (2% in both cases). It contains no saturated fat. The table also shows that 83% of the product can be considered to be dietary fibre, the greater part of which is characterised as soluble fibre.

The dossier reports the results of animal and human studies, which demonstrate that psyllium fibre binds to vitamins and minerals, thereby slightly reducing the amounts of these substances that are absorbed in the intestine. It is claimed that this reduction is marginal and not clinically relevant.

The VNV Committee is of the opinion that, from a nutritional point of view, PSH is comparable with other fibre products. Accordingly, it anticipates no specific nutritional problems.

Microbiological information

Microbiological analyses are carried out after the raw plant material arrives in the US. The material is tested for the presence of aerobic bacteria, yeasts, moulds, *E. coli*, *Salmonella*, *P. aeruginosa* and *S. aureus*. According to the first assessor, the results obtained from three batches meet the specifications (in accordance with USP 2006). Furthermore, they give no cause to doubt the microbiological purity of the product.

The VNV Committee concurs with this conclusion.

Toxicological information

The dossier assumes that PSH is excreted from the body largely unchanged. According to the applicant, studies suggest that up to 6% of ingested PSH is hydrolysed in the stomach, releasing l-arabinose that is usually absorbed and metabolised. Based on the results of *in vitro* studies and animal tests, the applicant concludes that a small fraction of this material is fermented. Given the limited number of human studies that have been conducted, there is insufficient data to support any further statements.

A series of toxicological studies showed that psyllium (fibre) has a low acute toxicity and that it is well-tolerated. The results of subchronic studies in experimental animals showed that pigmentation can develop in the epithelial cells lining the collecting ducts of the kidneys,

following intake of a psyllium product. The dossier reports that no such discolouration occurs following the administration of the PSH product prepared using the new process.
Clinical studies have demonstrated that daily doses of up to 30 g of psyllium (and psyllium fibre) are well-tolerated. The reported adverse effects were mild gastrointestinal symptoms, such as flatulence, bloating and diarrhoea. These symptoms, which were attributed to a high intake of fibre, resolved following the conclusion of the treatment. A comparable effect was observed in human studies following the consumption of other fibres, including wheat bran.

There are no details of any reproductive toxicity studies or genotoxicity studies.

The dossier mentions a number of publications which report on gastrointestinal problems (including oesophageal obstructions) following the use of a psyllium-containing supplement. These adverse effects were attributed to insufficient liquid intake and/or incorrect use of the product.

The VNV Committee has no questions about this part of the dossier.

Allergenicity

Previous publications on psyllium (and psyllium fibre) have reported incidences of allergenicity. According to the dossier, sensitisation has been reported in individuals who had frequent contact with psyllium in the course of their work, such as nurses, pharmacists and workers in pharmaceutical plants. In a few instances, the intake of psyllium-containing products was reportedly followed by respiratory tract complaints and, in rare cases, anaphylaxis. Over the course of time, the applicant has switched to a production process with an extra purification step (thereby boosting purity from 85% to 95%). The allergenic agent is thought to occur mainly in the portion of the seed beneath the husk. The company has also decided to include an allergenicity warning in the labels of products destined for use outside the EU. According to the applicant, the implementation of these measures was followed by a sharp reduction in the number of reports of allergy.

The VNV Committee concurs with the conclusion of the first assessor that consideration should be given to the question of allergenicity. The question of whether PSH should be listed on the packaging as a possible allergen will have to be considered in conjunction with the provisions of European Directive 2003/89/EC.

References

1 'Application for the Approval of Psyllium Seed Husk (PSH)', product dossier of Kellog Compagny (2007)

2 'Initial Assessment Report of the Application for the Authorisation of Psyllium Seed Husk (PSH) from Plantago ovata under Article 4 of the Novel Food Regulation (EC) No. 256/97', Food Safety Authority of Ireland (april 2008).

Additional sources:

3. 'Assessment report on *Plantago ovata* Forssk., seminis tegementum', EMEA/HMPC (2006)
4. 'Community monograph on *Plantago ovata* Forssk., semen', EMEA/HMPC(2006)
5. 'Voedingsvezel", Food and Consumer Product Safety Authority (Voedsel en Waren Autoriteit) (2007), via http://www.vwa.nl

De Commissie / The Committee

- Prof. dr. G.J. Mulder, *voorzitter / chairman*
  emeritus hoogleraar toxicologie, Universiteit Leiden
  professor emeritus toxicology, Leiden University
- Prof. dr. C.A.F.M. Bruijnzeel-Koomen
  hoogleraar dermatologie/allergologie; UMC Utrecht
  professor of dermatology/allergology; University Medical Centre Utrecht
- Ir. E.J. Kok
  toxicoloog; RIKILT Instituut voor Voedselveiligheid, Wageningen
  toxicologist; RIKILT, Institute of Food Safety, Wageningen
- Dr. C.F. van Kreijl
  moleculair-bioloog (gepensioneerd); RIVM Bilthoven
  molecular biologist (retired); National Institute of Public Health and the Environment, Bilthoven
- Dr. F.M. Nagengast
  gastro-enteroloog; UMC St Radboud, Nijmegen
  gastro-enterologist; University Medical Centre St Radboud, Nijmegen
- Dr. ir. J.M.A. van Raaij
  voedingsfysioloog; Wageningen Universiteit en Researchcentrum; RIVM Bilthoven
  food physiologist; Wageningen University and Research Centre; National Institute of Public Health and the Environment, Bilthoven
- Prof. dr. ir. G. Schaafsma
  hoogleraar voeding; Wageningen Universiteit en Researchcentrum
  professor of nutrition; Wageningen University and Research Centre
- Dr. G.J.A. Speijers
  toxicoloog (gepensioneerd); RIVM Bilthoven
  toxicologist (retired); National Institute of Public Health and the Environment, Bilthoven
- Prof. dr. W.J. Stiekema
  hoogleraar bioinformatica; Wageningen Universiteit en Researchcentrum
  professor of bioinformatics; Wageningen University and Research Centre
- Drs. A.I. Viloria Alebesque, *adviseur / advisor*
  Ministerie van VWS, Den Haag
  Ministry of Health, Welfare and Sport, The Hague
- Prof. dr. W.M. de Vos
  hoogleraar microbiologie; Wageningen Universiteit en Researchcentrum
  professor of microbiology; Wageningen University and Research Centre
- Dr. R.A. Woutersen
  toxicoloog, toxicologisch patholoog; TNO Kwaliteit van Leven, Zeist
  toxicologist, toxicologic pathologist; TNO Quality of Life, Zeist

Bureau Nieuwe Voedingsmiddelen, CBG/ Novel Foods Unit, MEB

- Dr. C.M.A. van Rossum, *beoordelaar voedselveiligheid / scientific assessor food safety*
- Dr. M. Rutgers, *beoordelaar voedselveiligheid / scientific assessor food safety*
- Ir. E. Ensink, *beoordelaar botanicals / scientific assessor botanicals*
- Drs. E. van Galen, *hoofd BNV/ head NFU*
- Mr F. Zaidi, *management assistent/ management assistant*

Samenvatting van het dossier / Summary of the dossier

Application for the Approval of Psyllium Seed Husk (PSH)

Under

Regulation (EC) No 258/97 of the European Parliament and of the Council of 27th January 1997 Concerning Novel Foods and Novel Food Ingredients

NON-CONFIDENTIAL

SUMMARY

November 7, 2007

APPLICATION FOR THE APPROVAL OF PSYLLIUM SEED HUSH (PSH)

Regulation (EC) No 258/97 of the European Parliament and of the Council of 27th January 1997 Concerning Novel Foods and Novel Food Ingredients

Table of Contents

List of Tables

APPLICATION FOR THE APPROVAL OF PSYLLIUM SEED HUSK (PSH)

Regulation (EC) No 258/97 of the European Parliament and of the Council of 27th January 1997 Concerning Novel Foods and Novel Food Ingredients

ADMINISTRATIVE DATA

Name and Address of Applicants/Manufacturers

The application is submitted by:

Kellogg Company
Lakeshore Drive
Airside Business Park, Swords
County Dublin, Ireland

Name and Address of Person(s) Responsible for Dossier

Name: Mr. Reg Fletcher
Title: Director Nutrition and Regulatory Affairs

Telephone: +353 (0) 18830616
Facsimile: +353 (0) 18830710
E-mail: Reg.Fletcher@kellogg.com

GENERAL INTRODUCTION

Kellogg Company seeks approval of psyllium seed husk (PSH) prepared from *Plantago ovata* for use as a novel food. Approval for the use of PSH is sought under Regulation (EC) No. 258/97 of the European Parliament and of the Council of 27th January 1997 concerning novel foods and novel food ingredients (hereafter referred to as EC 258/97) (European Parliament and the Council of the European Union, 1997). This submission has been prepared pursuant to the Commission Recommendation of 29 July 1997 concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients. PSH will be considered for approval under class 2, sub-class 2.1, pertaining to "complex novel foods which are not, or are derived from sources which have not, been genetically modified, and the source of the novel food has a history of use within the European Community." The application will be further considered under category (e) referring to, "foods and food ingredients consisting of or isolated from plants and food ingredients isolated from animals, except for foods and food ingredients obtained by traditional propagating and breeding practices and which have a history of safe use."

I SPECIFICATIONS OF PSH

The common name for the product is psyllium seed husk (PSH). PSH is also known as "Blond Psyllium, Indian Psyllium, or Ispaghula" in commerce (USP, 2006).

The 95% psyllium husk specifications are presented in Table I.5-1 and represent the end product specifications for the use of PSH as an ingredient in various food products. The specifications set out the requirements for the physical characteristics, the typical nutritional composition, the contaminant specifications, and the microbiological specifications.

Table I.5-1 Chemical and Physical Specifications for PSH

Parameter	Kellogg Company Specification[1]	Test Method
Physical characteristics		
Form	Free flowing powder	ST-120
Colour	Pale to medium buff with few dark flecks	ST-120
Odour	Faint characteristic odour	ST-120
Flavour	Bland mucilaginous taste	ST-120
Particle Size	U.S.S. Screens	Ro-Tap 25 g sample, 20 minutes with hammer
	On #30 1.0 % Max	ST-116
	On #40 5.0 % Max.	ST-116
	Thru #100 35.0 % Max.	ST-116
Bulk Density	Tapped Density (0.65 – 0.75 g/mL)	ST-115
Swell Volume	>50 ml/g	ST-256

Table I.5-1 Chemical and Physical Specifications for PSH		
Parameter	**Kellogg Company Specification[1]**	**Test Method**
Extraneous Matter	Light extraneous matter NMT 5%	ST-289
	Heavy extraneous matter NMT 1%	ST-289
Total Ash	3.5%	ST-288
Acid Insoluble Ash	1%	ST-288
Loss on Drying	<12.0%	ST-110
Foreign Materials		
Insects	No whole insects	ST-280
Metals		
Lead	<0.5 ppm	CSL Internal Method
Cadmium	<0.1 ppm	CSL Internal Method
Standard aerobic plate count	125,000/g Max.	MT-100
Yeasts and Moulds	4,000/g Max.	MT-100
Escherichia coli	<3 MPN/g	MT-100
Salmonella	None detected in 25 g	MT-100
Staphylococcus aureus	None detected in 25 g	MT-100
Pseudomonas aeruginosa	None detected in 25 g	MT-100

[1] Specifications developed by Kellogg for the use of PSH

[2] European Pharmacopeia or Food Chemical Codex specifications (or other food grade specifications)

The physical and chemical specifications listed in Table I.5-1 have been set by Kellogg Company and are in agreement with USP (2006) specifications.

The quality and adherence of PSH to the specifications laid out in Table I.5-1 were examined in 3 batches of 95% PSH. The samples from lot's 6A03/R-25168, 6A15/R-25365, and 6A15/R-25397 of 95% PSH were shown to meet the product specifications for PSH.

In addition to the analysis conducted on the physical and microbiological specifications for PSH further analyses were performed to determine the potential presence of mycotoxin (*e.g.*, ochratoxin A, aflatoxins, and trichothecenes) residues in PSH. PSH samples were also analysed for the presence of a wide variety of pesticide residues by the Central Science Laboratory (CSL) in accordance with an internal method for multi-residue analysis. No pesticide residues were detected at or above the detection limit of 0.01 ppm (mg/kg). Finally an analysis was performed on samples of PSH to determine the potential presence of heavy metals including arsenic, cadmium, mercury, and lead. The analysis demonstrated that heavy metals were present in amounts well below maximum levels set out in EU legislation.

The product is stored in a cool, dry area in well-closed containers, secured against insect attack.

II EFFECT OF THE PRODUCTION PROCESS APPLIED TO PSH

Psyllium seed is obtained from India and the husk is removed from the seed to be processed into PSH for use in various food and pharmaceutical products. The PSH consists of cells filled with mucilage, which is a white, fibrous material that is insoluble in alcohol, and swells with water to produce a thick solution (Anderson and Fireman, 1935). The composition of the mucilage depends largely on the method of preparation used. A low volume of water for a short time and little force in pressing the solution through a sieve leads to the production of small quantities of mucilage with high ash, high uronic acid, and low pentosan content. The use of a higher volume of water, longer extraction time, and greater pressure to force the solution through the sieve results in the production of mucilage with lower ash and lower uronic acid content, but higher pentosan content. Additional extractions result in the production of a final product with a higher total amount of mucilage.

The mucilage from PSH cells consists of a mixture of polyuronides that are composed of *d*-galacturonic acid combined with *l*-arabinose (Anderson and Fireman, 1935). Molecules of *d*-xylose varying in length from 8 to 35 molecules are combined with *l*-arabinose along with insoluble material remaining after hydrolysis of the mucilage (termed an X body).

Food-grade water and citric acid is used in compliance with local hygiene regulations.

Psyllium harvested in India undergoes mechanical separation of the PSH from the seed itself in a grinding mill with successive grades of purity of PSH formed in attrition mills. The separated PSH is bagged for shipment and sent for processing and blending in the United States (US) where the raw material is tested for moisture, protein, ash (total and acid insoluble), swell volume, light extraneous matter, particle size after milling, bulk density, and microbiological parameters (see Table I.5-1). All methods used to examine the raw PSH comply with United States Pharmacopeia (USP) standards and the acceptability of each lot is judged against pre-established specifications.

The quality of PSH is determined by the amount of extraneous matter present. Extraneous matter is classified as either light extraneous matter or heavy extraneous matter. Light extraneous matter is the main contributor of extraneous matter in PSH. It consists of agricultural impurities and agricultural produce other than the husks (which includes the psyllium seeds). Light extraneous matter is determined according to the procedure in the USP (USP 29, pg. 1863), which measures the amount of material that floats on the surface of trichloroethylene (chloroform is a suitable substitute). The USP 29 specification is no more than (NMT) 5% light extraneous matter (Kellogg specification is NMT 5.0%).

III HISTORY OF THE SOURCE ORGANISM OF PSH – *PLANTAGO OVATA*

Plantago ovata, also referred to commonly as psyllium and ispaghula, is the source organism for the production of PSH. It is primarily grown in India, the United States, and southern Europe and cultivated primarily for its use in laxatives in North America and Australia and dietary/food supplements in Europe and North America as FyboGel™, Regulan™ and Metamucil™. The seed contains the bioactive mucilage polysaccharide; however, the refined psyllium seed husk known as Ispaghula husk is principally used as the fibre source in the production of laxatives, nutritional supplements, and ready-to-eat cereals (RTCs).

PSH is present in Kellogg's All-Bran Buds® RTC in Canada and the United States (US). In Australia PSH is present in a number of cereal products including Kellogg's GUARDIAN Oat Puffs, as well as Freedom Foods Ultra-Rice with psyllium, Rice Puffs with Psyllium, Rice Flakes with Psyllium, and Gluten Free Wheat Free MUESLI with psyllium. Furthermore, PSH is available in capsule, granule, or powder (for reconstitution) form for use as a dietary supplement in Canada and the United States (PDRNS, 2001). Similarly, PSH is available as a medicinal supplement in Germany for use in the treatment of chronic constipation, various forms of diarrhoea, and irritable bowel syndrome. PSH has been available throughout the European Union (EU) in over-the-counter (OTC) pharmaceuticals and food supplements for a number of years.

IX ANTICIPATED INTAKE/EXTENT OF USE OF PSH

Kellogg's is seeking approval to market breakfast cereals and associated products in the EU fortified with PSH. The products will be marketed on the basis of the nutritional benefits of PSH including as a good source of dietary fibre, stool bulking properties, reduced glycaemic response (glycaemic index), cholesterol management and/or moderating satiety. The proposed product categories, individual food uses and the use level of PSH in the various food products are outlined in Table IX.I-1. The target addition level for PSH is up to 3.5 g per serving and assumptions have been made based on the average of typical serving sizes set out by the Food Standards Agency (FSA) in the third edition of the FSA (2002) guide to "Food Portion Sizes", to present this in terms of % w/w (g/100g) for convenience.

Table IX.1-1 Summary of the Individual Food Uses and Use-Levels for PSH in the European Union		
Food Category	**Proposed Food-Use**	**Use-Level (%)**
Cereals and Cereal Products	*Breakfast Cereals*	
	Breakfast Cereals	12
	Cereal Bars	
	Cereal Bars	12

Food codes representative of each proposed food-use were chosen from the Ministry of Agriculture, Fisheries, and Food (MAFF) food code list associated with each food consumption survey and grouped in food-use categories according to the food type, main and subsidiary food group classifications detailed within the National Diet and Nutrition Survey (NDNS) reports (UKDA, 1991, 1995, 2001).

The potential intake of PSH is estimated using food consumption data generated by the United Kingdom (UK) FSA Dietary Survey Programme (DSP). The MAFF and the Department of Health were responsible for the joint commission of the NDNS program in 1992. The responsibility for the program was subsequently transferred from MAFF to the FSAupon its inception in April 2000. The NDNS programme itself consists of four different surveys targeting specific age groups, which were conducted every 3 years in succession. Separate survey data are available from the U.K. Data Archive (UKDA) for the NDNS: Adults Aged 16 to 64 years collected in 2000-2001 (NDNS, 2000-2001) (Office for National Statistics, 2005), the National Diet, Nutrition and Dental Survey of Children Aged 1½ to 4½ Years, 1992-1993 (NDNS, 1992-1993) (UKDA, 1995), the National Diet and Nutrition Survey: Young People aged 4 to 18 Years (NDNS, 1997) (UKDA, 2001), and the National Diet and Nutrition Survey: People Aged 65 Years and Over, 1994-1995. Although all 4 surveys are available, only the first and third were utilised in the generation of estimates in the current intake analysis. When combined, the survey results provide the most current data for use in the evaluation of food-use, food-consumption patterns, and nutritional status for individuals residing within the U.K. Weighted 4- or 7-day food records for individuals were selected using a stratified multi-stage random probability design, with sampling of private households throughout Great Britain using postal sectors (UKDA, 1995, 2001; Office for National Statistics, 2005) as the primary sampling unit.

Table IX.2.1-1 Summary of the Estimated Daily Intake of PSH from All Proposed Food Categories in the U.K. by Population Group (NDNS Data)

Population Group	Age Group (Years)	% User	Actual # of Total Users	All-Person Consumption				All-Users Consumption			
				Mean (g)	Percentile (g)			Mean (g)	Percentile (g)		
					90	95	97.5		90	95	97.5
Young People	4-10	90.1	754	2.96	5.95	7.10	8.42	3.25	6.02	7.30	8.74
Female Teenagers	11-18	68.4	305	2.18	5.52	7.61	9.74	3.11	6.17	8.55	10.68
Male Teenagers	11-18	80.3	334	3.99	8.71	10.56	12.94	4.88	9.19	11.26	14.71
Female Adults	16-64	62.0	594	2.30	5.98	7.58	9.26	3.54	7.10	8.57	10.65
Male Adults	16-64	57.4	440	2.89	8.02	10.46	12.86	4.80	9.97	11.81	14.29

Table IX.2.1-2 Summary of the Estimated Daily Per Kilogram Body Weight Intake of PSH from All Proposed Food Categories in the U.K. by Population Group (NDNS Data)

Population Group	Age Group (Years)	% User	Actual # of Total Users	All-Person Consumption				All-Users Consumption			
				Mean (mg/kg)	Percentile (mg/kg)			Mean (mg/kg)	Percentile (mg/kg)		
					90	95	97.5		90	95	97.5
Young People	4-10	90.1	754	116	238	288	325	128	246	294	328
Female Teenagers	11-18	68.4	305	41	112	146	178	61	130	164	193
Male Teenagers	11-18	80.3	334	75	168	208	247	92	176	223	256
Female Adults	16-64	62.0	594	32	89	114	134	52	104	130	154
Male Adults	16-64	57.4	440	33	97	119	156	58	116	150	192

The greatest all-user consumption of PSH among the different population groups was determined to occur in male teenagers with a 97.5th percentile intake of 14.71 g PSH/ person/day (approximately 5 to 6 daily portions), while the greatest all-user consumption on a body weight basis was estimated in young people with a 97.5th percentile intake of 0.33 g PSH/kg body weight/day.

X INFORMATION FROM PREVIOUS HUMAN EXPOSURE TO PSH OR *PLANTAGO OVATA*

PSH does not typically occur naturally in the European diet but has been used for a number of years throughout Canada, the US, the EU, Australia, and many other countries for the relief/treatment of constipation and/or irregular bowel movements in the form of a PSH hydrocolloid in Metamucil®. Food supplements containing PSH are widely available in health food stores in the UK, with typical daily recommendations of 10 g, often taken as a drink. It is estimated that approximately 4 million people in the US had been exposed to low levels of PSH for up to 20 years. The recommended consumption of PSH hydrocolloid is 428 mg/kg body weight/day (approximately 20 to 25 g) of PSH for 1 week or less.

The potential allergenicity of PSH has been addressed in section XIII in relation to human safety. Furthermore, the reduction of the potential for the presence of any allergenic material in manufactured PSH has been addressed in section II.

XI NUTRITIONAL INFORMATION ON PSH

The typical nutritional composition profile for PSH is illustrated in Table XI.1.

Table XI.1-1 Typical Nutritional Composition for PSH

Parameter	Kellogg Company Specification (g)
Ash	2.05
Dietary Fibre	83.0
Insoluble Fibre	11.5
Soluble Fibre	72.0
Potassium	1.70
Protein	2.0
Saturated Fat	0.0
Total Carbohydrate	84.27
Total Fat	2.0

The typical nutritional profile illustrates that PSH is low in fat, especially saturated fat and is very high in carbohydrates, dietary fibre, and soluble fibre. An appreciable amount of insoluble fibre is present within PSH, as well as lesser amounts of ash, protein, total fat, and potassium.

Psyllium seed husk will be used, in part, to replace existing sources of dietary fibre and, in part, it will contribute an additional source of fibre in the diet.

PSH is a rich source of dietary fibre, which has been demonstrated to be particularly effective at delivering the benefits associated with dietary fibre. The associated benefits include: stool bulking and ease of laxation; cholesterol reduction and reduced risk of coronary heart disease; reduced glycaemic control and improved insulin sensitivity; and increased satiety and weight control.

In the EU there are no specific labelling requirements governing the labelling of products containing PSH. The labelling of PSH falls under general considerations in Directive 2000/13/EC and is not captured within the allergen labelling Directive 2003/89/EC. Although there are no specific regulations governing the inclusion of a warning label regarding the presence of PSH in the product it would be prudent to include such a label to safeguard the health of the consumers that may be allergic. Further discussion on the allergenic potential of PSH is provided in Section XIII.

The US Food and Drug Administration (FDA) requires specific labelling for products containing PSH in order to minimize the potential for minor adverse occurrences. In products to which PSH is incorporated the labels must abide by the following:

> (1) Foods containing dry or incompletely hydrated psyllium husk, also known as psyllium seed husk, and bearing a health claim on the association between soluble fibre from psyllium husk and reduced risk of coronary heart disease, shall bear a label statement informing consumers that the appropriate use of such foods requires consumption with adequate amounts of fluids, alerting them of potential consequences of failing to follow usage recommendations, and informing persons with swallowing difficulties to avoid consumption of the product (*e.g.*, "NOTICE: This food should be eaten with at least a full glass of liquid. Eating this product without enough liquid may cause choking. Do not eat this product if you have difficulty in swallowing."). However, a product in conventional food form may be exempt from this requirement if a viscous adhesive mass is not formed when the food is exposed to fluids.

As stated in the final sentence, products that contain PSH, but are in conventional food form are not required to carry any specific warnings related to potential obstruction and adequate water consumption as long as, "….a viscous adhesive mass is not formed when the food is exposed to fluids."

The label will clearly inform consumers of the presence of PSH and advise any PSH-sensitive consumers to avoid the product as it contains PSH.

XII MICROBIOLOGICAL INFORMATION ON PSH

Microbiological specifications for PSH ready for inclusion into various food products are presented in Table I.5-1. Furthermore, the analysis of 3 batches of 95% PSH demonstrates its adherence to the microbiological specifications outlined for PSH.

XIII TOXICOLOGICAL INFORMATION ON PSH

The metabolism of PSH is not well characterized in humans or animals; however, PSH has been demonstrated to be hydrolyzed to a limited extant (*i.e.*, approximately 1 to 6%) in the stomachs of human volunteers thereby resulting in the release of free arabinose (Andersen *et al*., 1988). The stomach has been reported to be the sole location for the hydrolysis of PSH with no additional decomposition of PSH occurring in the small bowel of human subjects. In addition to the limited hydrolysis of PSH in the stomach, fermentation of PSH is expected to occur in the large bowel. PSH has been reported to increase faecal mass, faecal bulk, total faecal weight, the number of daily bowel movements, the wet and dry weight of stools, and decrease transit time (BeMiller, 1973; Prynne and Southgate, 1979; Stevens *et al*., 1988; Cummings, 1993).

In vitro colonic cell cultures from African green monkeys fed PSH have been demonstrated to produce higher concentration of short chain fatty acids (SCFAs), have a lower pH, and a lower ratio of anaerobes to aerobes compared to cultures from monkeys fed cellulose (Costa *et al*., 1998a). Similarly, colonic cells from human subjects incubated with PSH were reported to have higher SCFA production compared to colonic cells incubated with cellulose (Haynes and Lupton, 1989). Furthermore, *in vivo* studies in rats and monkeys have demonstrated that PSH is fermented to varying extents resulting in higher production of SCFA and increased faecal bacterial mass (Costa *et al*., 1989a; Leng-Peschlow, 1991; Edwards *et al*., 1992). Studies on the fermentation of PSH in human volunteers have demonstrated varying degrees of apparent digestibility, while the majority of the studies suggested that PSH was not fermented in the human bowel due to the absence of breath hydrogen, methane, and serum acetate (Salyers *et al*., 1978; Prynne and Southgate, 1979; Horvath *et al*., 1983; McBurney and Thompson, 1989; Tomlin *et al*., 1989; Gibson *et al*., 1990; Clausen *et al*., 1991). The apparent difference between the *in vitro* and *in vivo* results with PSH (*i.e.*, the absence of fermentation of PSH *in vivo*) may be due to 25% of PSH preparations (Metamucil®) being available as carbohydrate, which would be absorbed in the small intestine and therefore be unavailable to the colonic microorganisms (McBurney and Thompson, 1989).

Preclinical studies demonstrated that PSH was relatively well-tolerated in various animal species with few, if any untoward effects. PSH was orally administered to rats, cats, and dogs at dosages of up to 1.0 g/kg body weight/day. No treatment-related deaths occurred in any of the subchronic or chronic studies; however, minor effects such as the appearance of fine dark granules in kidney tubules and in the epithelial cells of kidney tubules were apparent in rats and

cats (MacKay *et al*., 1932; Thienes and Hall, 1941; Coulston and Seed, 1956). Kidney function and weight gain were unaffected in the animals. The pigmentation observed in the kidneys (*i.e.*, in the epithelial cells of the kidney tubules and the collecting tubules) was attributed to the botanical fraction of the hull of the seed, which would be removed from preparations of PSH meant for human consumption (Coulston and Seed, 1956).

Although no preclinical studies specifically designed to evaluate the potential carcinogenicity of PSH have been conducted, 13 studies ranging in duration from 5 months to lifetimes of the animals have been conducted in various species fed PSH (Thienes and Hall, 1941; Carlson and Hoelzel, 1948; Buth and Mehta, 1983; Paulini *et al*., 1987; Costa *et al*., 1989a,b; Richter and Schneeman, 1990; Schneeman and Richter, 1990, 1993; McCall *et al*., 1992a,b). The aims of these studies were to evaluate endpoints other than carcinogenicity; however, there was no mention of tumourigenesis in any of these studies. Furthermore, the potential effect of PSH on the tumourigenicity of carcinogens was examined in a small number of studies (Toth, 1984; Roberts-Andersen *et al*., 1987; Wilpart and Roberfroid, 1987; Alabaster *et al*., 1993). With the exception of Toth (1984), the administration of PSH as part of the diet has been demonstrated to be protective against the effect of known carcinogens with respect to the incidence of intestinal and colonic tumours, as well as the number of tumours per group. Toth (1984) reported that PSH increased the carcinogenicity of 1,2-dimethylhydrazine dihydrochloride (DMH) when in fact male Swiss mice administered PSH were demonstrated to have a lower incidence of colon tumours (*i.e.*, an incidence of 8:50 and 19:50 tumours in mice fed PSH and DMH compared to mice fed DMH alone) (Roberts-Andersen *et al*., 1987). The protective effect of PSH was suggested to be due to the production of SCFAs.

The potential effects of PSH in human subjects has been evaluated through the ingestion of PSH in short- and long-term clinical trials with hospitalized patients and healthy subjects provided oral dosages of PSH or PSH mucilloid (*i.e.*, Metamucil®) (Thienes and Hall, 1941; Beher *et al.*, 1973; Brydon *et al.*, 1979; Spiller *et al*., 1979; Sölter and Lorenz, 1983; Stoy *et al*., 1993). PSH was ingested by patients and healthy subjects for periods ranging from 6 days to 7 years with no reports of serious adverse effects. Thienes and Hall (1941) reported that PSH ingestion in 9 people consuming 7 to 14 g/day of PSH flakes over 2 to 7 years had no adverse effects, and specifically no effect on kidney function. Similarly, in a double blind placebo-controlled study with 50 healthy individuals ingesting 20 g of a PSH preparation per day for 20 days, no adverse effects were reported with respect to blood chemistry and haematology (Spiller *et al*., 1979). Minor adverse effects were reported among some subjects; however, the adverse effect rates were similar between the PSH, cellulose-pectin, and placebo groups. Other trials involving the ingestion of PSH by patients with uncomplicated gallstone disease or post-cholecystectomy demonstrated no adverse effects (Beher *et al.*, 1973; Brydon *et al*., 1979). Furthermore, the use of PSH hydrocolloid for relief of chronic constipation and bowel irregularity was reported to result in the occurrence of mild side effects in some subjects (Sölter and Lorenz, 1983).

Although there are few published pre-clinical studies examining the safety of PSH consumption, there are numerous human clinical studies and case reports examining the safety, efficacy, and tolerability of PSH. Various studies examining the efficacy of PSH in the treatment/mitigation of the symptoms of IBS and hypercholesterolemia, as well as in the management of blood glucose levels in type II diabetics demonstrated that PSH is relatively well tolerated by healthy and health-compromised individuals. Side effects reported in a few of the trials were typical of the effects of consuming large amounts of soluble dietary fibre (*i.e.*, mild gastrointestinal symptoms including flatulence, bloating, diarrhoea, *etc*.) and were resolved following the discontinuation of the treatment.

Additional studies in humans examined the potential effect of PSH consumption on vitamin and mineral status. Slight alterations were reported in mineral and vitamin levels; however, the effects were rarely significant and in instances where the mineral or vitamin levels were significantly altered the alterations were statistically significant, but not biologically significant. The significant changes were typically observed in studies of shorter durations, while mineral and vitamin parameters usually stabilized within normal values during studies of longer duration. It is important to note that the PSH was consumed in a concentrated dose rather than as part of a food matrix. Animal studies examining the potential effect of PSH on vitamin and mineral parameters confirmed the results observed in human studies.

Aside from potential gastrointestinal symptoms associated with the consumption of high levels of dietary fibre oesophageal and gastrointestinal obstruction have been reported in the literature. The occurrences of oesophageal and gastrointestinal obstruction have been reported to occur with the consumption of the powdered form of PSH for use as a laxative. The primary cause of these occurrences of oesophageal and gastrointestinal obstruction has been identified as a lack of proper hydration and misuse of the product (*i.e.*, improper use due to not following the instructions). Although oesophageal and gastrointestinal obstruction are potentially serious side effects to the consumption of PSH the only case reports have occurred with the ingestion of the powdered form and not with any food product manufactured with PSH within the food itself. It has been suggested that the manufacture of food products containing PSH results in adequate hydration of PSH and therefore negates the potential for swelling of PSH within the oesophagus or the gastrointestinal system.

The potential allergenicity of PSH represents a risk to a small segment of the population. The allergenic substance has been demonstrated to be contained in the gum and protein fraction of the seed itself, rather than within the husk, which is the portion of *Plantago ovata* to be consumed. The reduction in the potential allergenicity of PSH was attributed to the production a higher quality PSH, which minimized the potential presence of the allergenic substance and reduced the number of allergic reactions from June 1990 to September 1992 according to Talbot *et al.* (1993). The vast majority of published case reports of allergic reactions to PSH have occurred in nurses, pharmaceutical plant workers, and pharmacists that are exposed to

PSH dust during the preparation of PSH-containing laxative formulations or during the processing of PSH in pharmaceutical plants. In these professions the individuals that have reported adverse reactions (*e.g.*, congestion, wheezing, etc.) and serious adverse reactions (*e.g.*, anaphylaxis) have experienced sensitization due to their previous exposures to PSH powder. These individuals appeared to have developed hypersensitivity to PSH *via* inhalation of the powder which resulted in an allergic reaction when challenged by the presence of the allergenic substance in the highly purified PSH present in Heartwise® cereal. These individuals represent a small portion of the population and the vast majority of people are unlikely to experience an allergic reaction due to the presence of the potentially allergenic substance unless prior sensitization has occurred. As a result proper labelling (*e.g.*, similar to the label used on Heartwise® cereal) to inform at risk individuals of the potential hazards of the consumption of PSH-containing products should be sufficient to prevent any serious adverse reactions. Individuals in healthcare or in the manufacture of PSH that are perhaps unaware of their sensitization to PSH will be informed of their potential for an allergic reaction due solely to their employment.

Based on the foregoing toxicological studies and the proposed intake level, the consumption of PSH is not expected to present any significant risk to the health of consumers.

REFERENCES

Alabaster, O.; Tang, Z.C.; Shivapurkar, N. 1993. Protective effect of wheat bran-psyllium combinations on the formation of colon tumours in rats on high fat, low calcium diets. FASEB J 7(4, Part II):A722 [Abstract No. 4174].

Andersen, J.R.; Bukhave, K.; Hojaard, L.; Rasmussen, H.S.; Hermansen, N.; Worning, H.; Krag, E. 1988. Decomposition of wheat bran and ispaghula husk in the stomach and small intestine of healthy men. J Nutr 118:326-331.

Anderson, E.; Fireman, M. 1935. The mucilage from psyllium seed, plantago psyllium, L. Am J Pharm 107:437-442.

Beher, W.T.; Schuman, B.M.; Block, M.A.; Lin, G.J.; Casazza, K.K. 1973. The effect of psyllium hydrocolloid and cholestyramine on hepatic bile lipid consumption in man. Henry Ford Hosp Med J 21(1):21-30.

Bell, L.P.; Hectorne, K.; Reynolds, H.; Balm, T.K.; Hunninghake, D.B. 1989. Cholesterol-lowering effects of psyllium hydrophilic mucilloid. JAMA 261:3419-3423.

BeMiller, J.N. 1973. Quince seed, psyllium seed, flax seed, and okra gums. In: Whister, R.L.; BeMiller, J.N., (Eds.). Industrial Gums: Polysaccharides and Their Derivatives (2nd Ed.). Academic Press; New York, pp. 339-367.

Brydon, W.G.; Borup-Christensen, S.; Van der Linden, W.; Eastwood, M.A. 1979. The effect of dietary psyllium hydrocolloid and lignin on bile. Z Ernahrungswiss 18(2):77-80.

Buth, M.; Mehta, T. 1983. Effect of psyllium husk on iron bioavailability in monkeys. Nut Rep Int 28(4):743-752.

Carlson, A.J.; Hoelzel, F. 1948. Prolongation of the life span of rats by bulk-formers in the diet. J Nutr 36:27-40.

Clausen, M.R.; Bonnén, H.; Mortensen, P.B. 1991. Colonic fermentation of dietary fibre to short chain fatty acids in patients with adenomatous polyps and colonic cancer. Gut 32:923-928.

Costa, M.A.; Mehta, T.; Males, J.R. 1989a. Effects of dietary cellulose and psyllium husk on monkey colonic microbial metabolism in continuous culture. J Nutr 119(7):979-985.

Costa, M.A.; Mehta, T.; Males, J.R. 1989b. Effects of dietary cellulose, psyllium husk and cholesterol level on faecal and colonic microbial metabolism in monkeys. J Nutr 119(7):986-982.

Coulston, F.; Seed, J.C. 1956. The relationship of Psyllium seed and various fractions of the seed to kidney pigmenta. J Am Pharm Assoc Sci Ed 45:716-719.

Cummings, J.H. 1993. The effect of dietary fibre on faecal weight and composition. In: Spiller, G.A. Dietary Fibre in Human Nutrition (2nd Ed.). CRC Press; Boca Raton, pp. 263-349.

Edwards, C.A.; Bowen, J.; Brydon, W.G.; Eastwood, M.A. 1992. The effects of ispaghula on rat caecal fermentation and stool output. Br J Nutr 68(2):473-482.

European Parliament and the Council of the European Union. 1997. Regulation EC No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients. Off J Eur Communities 40(L43):1-7.

FCC. 2003. Citric acid. In: Food Chemicals Codex (5th Ed.). National Academy Press; Washington, DC, pp. 115-116.

FSA. 2002. Food Portion Sizes (3rd Ed.). Food Standards Agency (FSA), Her Majesty's Stationery Office (HMSO); London, Engl.

Gibson, G.R.; MacFarlane, S.; Cummings, J.H. 1990. The fermentability of polysaccharides by mixed human faecal bacteria in relation to their suitability as bulk-forming laxatives. Lett Appl Microbiol 11:251-254.

Haynes, S.R.; Lupton, J.R. 1989. The effects of cellulose and psyllium supplementation on short chain fatty acid profiles in healthy females. FASEB J 3:A1069 [Abstract No. 4897].

Horvath, P.J.; Jersci, J.L.; Fadel, J.G.; Van Soest, P.J. 1983. Rate of gas released by human fecal fermentation of dietary fibre. Fed Proc 42(3):675 [Abstract No. 2241]..

Leng-Peschlow, E. 1991. *Plantago ovata* seeds as dietary fibre supplement: Physiological and metabolic effects in rats. Br J Nutr 66(2):331-349.

MacKay, E.M.; Hall, E.M.; Smith, F.M. 1932. Renal pigmentation following ingestion of psyllium seed. Proc Soc Exp Biol Med 30:152-155.

McBurney, M.I.; Thompson, L.U. 1989. In vitro fermentabilities of purified fibre supplements. J Food Sci 54(2):347-350.

McCall, M.R.; Mehta, T.; Leathers, C.W.; Foster, D.M. 1992a. Psyllium husk. I: Effect on plasma lipoproteins, cholesterol metabolism, and atherosclerosis in African green monkeys. Am J Clin Nutr 56(2):376-384.

McCall, M.R.; Mehta, T.; Leathers, C.W.; Foster, D.M. 1992b. Psyllium husk. II: Effect on the metabolism of apolipoprotein B in African green monkeys. Am J Clin Nutr 56(2):385-393.

Office for National Statistics. 2005. The National Diet and Nutrition Survey: Adults Aged 19 to 64 Years: 2000-2001 [Computer File]. Office for National Statistics, Social and Vital Statistics Division & Food Standards Agency (FSA); Colchester, Essex, UK, UK Data Archive [distributor]. SN: 5140.

Paulini, I.; Mehta, T.; Hargis, A. 1987. Intestinal structural changes in African Green monkeys after long term psyllium or cellulose feeding. J Nutr 117:253-266.

PDRNS. 2001. Psyllium. In: PDR® for Nutritional Supplements (1st Ed.). Physicians' Desk Reference (PDR); Demoines, Iowa/Medical Economics Data Production Company; Montvale, New Jersey, pp. 384-386. Available from: http://www.pdrhealth.com/drug_info/nmdrugprofiles/nutsupdrugs/psy_0214.shtml.

Pyrnne, C.J.; Southgate, D.A.T. 1979. The effects of a supplement of dietary fibre on faecal excretion by human subjects. Br J Nutr 41:495-503.

Richter, R.D.; Schneeman, B.O. 1990. Long-term feeding of oat bran, wheat bran, or psyllium husk: Effect on rat plasma and liver lipids. FASEB J 4(3, Part 1):A528 [Abstract No. 1515].

Roberts-Andersen, J.; Mehta, T.; Wilson, R.B. 1987. Reduction of DMH-induced colon tumours in rats fed psyllium husk or cellulose. Nutr Cancer 10:129-136.

Salyers, A.A.; Harris, C.J.; Wilkins, T.D. 1978. Breakdown of psyllium hydrocolloid by strains of *Bacteriodes ovatus* from the human intestinal tract. Can J Microbiol 24:336-338.

Schneeman, B.O.; Richter, D. 1990. Long-term feeding of oat bran, wheat bran, or psyllium husk: Effects on the gastrointestinal tract. FASEB J 4(3, Part 1):A528 [Abstract No. 1516].

Schneeman, B.O.; Richter, D. 1993. Changes in plasma and hepatic lipids, small intestinal histology and pancreatic enzyme activity due to aging and dietary fibre in rats. J Nutr 123(7):1328-1337.

Spiller, G.A.; Shipley, E.A.; Chernoff, M.C.; Cooper, W.C. 1979. Bulk laxative efficacy of a psyllium seed hydrocolloid and of a mixture of cellulose and pectin. J Clin Pharmacol 19(5&6):313-320.

Sölter, H.; Lorenz, D. 1983. Summary of clinical results with Prodiem™ Plain, a bowel-regulating agent. Today's Ther Trends. Cited In: Talbot *et al*. (1993).

Stevens, J.; VanSoest, P.J.; Robertson, J.B.; Levitsky, D.A. 1988. Comparison of the effects of psyllium and wheat bran on gastrointestinal transit time and stool characteristics. J Am Diet Assoc 88:323-326.

Stoy, D.B.; LaRosa, J.C.; Brewer, B.K.; Mackey, M.; Meusing, R.A. 1993. Cholesterol-lowering effects of ready-to-eat cereal containing psyllium. J Am Diet Assoc 93(8):910-912.

Talbot, J.M.; Anderson, S.A.; Fisher, K.D. 1993. The Evaluation of the Safety of Psyllium Seed Husk as a Food Ingredient. Prepared for Kellogg Company, Battle Creek, Mich. by Federation of American Societies for Experimental Biology (FASEB), Life Sciences Research Office (LSRO); Bethesda, Maryland.

Thienes, C.H.; Hall, E.M. 1941. On pigmentation of kidneys by psyllium and its effects on excretion: An experimental and clinical study. Am J Dig Dis 8(8):307-309.

Tomlin, J.; Taylor, J.S.; Read, N.W. 1989. The effects of mixed faecal bacteria on a selection of viscous polysaccharides in vitro. Nutr Rep Int 39:121-135.

Toth, B. 1984. Effect of Metamucil on tumour formation by 1,2-dimethylhydrazine dihydrochloride in mice. Food Chem Toxicol 22(7):573-578.

UKDA. 1991. Dietary and Nutritional Survey of British Adults, 1986-1987 [computer file]. Office of Population Censuses and Surveys, Social Survey Division, Ministry of Agriculture, Fisheries and Food (MAFF), and Department of Health. Colchester, Essex; UK Data Archive (UKDA) [distributor], 18 September 1991. SN: 2836.

UKDA. 1995. National Diet, Nutrition and Dental Survey of Children Aged 1 ½ to 4 ½ Years, 1992-1993 [computer file]. Office of Population Censuses and Surveys, Social Survey Division, Medical Research Council Centre for Human Nutrition Research, Ministry of Agriculture, Fisheries and Food (MAFF), and U.K. Department of Health. Colchester, Essex; UK Data Archive (UKDA) [distributor], 13 December 1995. SN: 3481.

UKDA. 2001. National Diet and Nutrition Survey: Young People Aged 4 to 18 Years, 1997. Office for National Statistics Social Survey Division, Medical Research Council Centre for Human Nutrition Research, Ministry of Agriculture, Fisheries and Food (MAFF), and Department of Health. Colchester, Essex; UK Data Archive (UKDA) [distributor], 25 January 2001. SN: 4243.

USP. 2006. United States Pharmacopeia (29th Ed.) & National Formulary (24th Ed.). U.S. Pharmacopeia (USP) Convention Inc.; Rockville, Maryland, pp. 1863-1864.

Wilpart, M.; Roberfroid, M. 1987. Intestinal carcinogenesis and dietary fibers: The influence of cellulose or Fybogel chronically given after exposure to DMH. Nutr Cancer 10(1&2):39-51.

Eerste beoordeling / First assessment

Initial Assessment Report of the Application for the Authorisation of Psyllium Seed Husk (PSH) from *Plantago ovata* under *Article 4* of the Novel Food Regulation (EC) No. 258/97

Name of Applicant: Kellogg Company, Ireland

Contact person(s): Mr Reg Fletcher, Kellogg Company and Mr Nigel Baldwin, Cantox.

Novel Food Classification: 2.1.

Introduction

An application for the authorisation of Psyllium Seed Husk (PSH) as a novel food ingredient under *Article 4* of the novel food Regulation (EC) No. 258/97 was submitted to the Food Safety Authority of Ireland (FSAI) in September of 2007. The dossier was formally accepted by the FSAI on November 26th, 2007 by letter to Mr. Reg Fletcher of Kellogg Company Ireland, and copied to Mr. Andreas Klepsch of the European Commission.

The application for the authorisation of PSH was prepared pursuant to Commission Recommendation 97/618/EC concerning the scientific aspects and the presentation of information in support of an application to market novel foods and novel food ingredients in the EU. PSH is considered for approval by the applicant in the category of "food and food ingredients consisting of, or isolated from plants, and food ingredients isolated from animals, except for foods and food ingredients obtained by traditional propagating or breeding practices and having a history of safe food use" (*Article 1.*2.(e) of Regulation (EC) No. 258/97). In order to assess wholesomeness, PSH is considered by the applicant to be in Class 2.1; "Complex novel food from non-GM source which has a history of food use in the community" (Commission Recommendation 97/618/EC).

PSH contains a high proportion of hemicellulose and its main role in the plant is to protect the Psyllium seed and prevent dehydration. PSH is firstly separated from Psyllium seeds (*Plantago ovata*) that are harvested in India and then processed in the USA to a blend suitable for food use.

PSH is already used as an ingredient in a number of foodstuffs in countries including the US, Canada and Australia. However, its only use in the EU, to date, has been as an ingredient in food supplements taken for the relief of constipation or irregular bowel movement. A number of EU Member States classify foods containing PSH as medicinal products. A novel food authorisation is required in this case because, in the EU, a history of consumption of an ingredient in food supplements is not sufficient to allow the use of that ingredient in general foodstuffs without a novel food authorisation (Standing Committee for the Food Chain and Animal Health, February 14, 2005). The applicant clarified that the intention is to use PSH in the fortification of breakfast cereals and cereal bars only.

Using the schemes outlined in Commission Recommendation 97/618/EC, the information addressing the safety of PSH is set out as follows.

I. Specification of the novel food

Psyllium Seed Husk (PSH) is the common name for the novel food ingredient, which is derived from the protective layer of material surrounding the seed of *Plantago ovata,* also known as Ispaghula, Blond Psyllium or Indian Psyllium. The novel ingredient is a pale coloured, free-flowing powder with some flecks, and has a faint odour and bland mucilaginous taste. The husk has a high content of hemicellulose comprising a xylan backbone linked to units of arabinose, rhamnose and galacturonic acid. The three batch analyses (Table I.6-1 of the application dossier) with certificates (Annex A of the application dossier) demonstrate the adherence of the final product to the physical and chemical specifications of PSH as presented in Table I.5-1 of the application dossier. Though the analysis is carried out at the time of entry of the raw ingredient to the US, subsequent processing is not likely to alter those specifications appreciably.

The final PSH product (95% pure) contains no more than 5% light extraneous matter (agricultural impurities) and not more than 1% heavy extraneous matter. Levels of microbial, heavy metal, pesticide and mycotoxin contaminants are within acceptable limits.

II. Effect of the production process applied to the novel food

The manufacturing process for PSH is represented in Figure II.2-1 of the application dossier. Following harvesting in India, the initial processing involves a mechanical disruption and separation of PSH from the PSH-seed complex. This is followed by a milling process, through which PSH is further purified. Compliance with product specification is determined for raw PSH on arrival in the US from India for further processing and blending. Processing in the US includes the use of food-grade water and food-grade citric acid, resulting in 95% pure PSH, and is not likely to alter the specifications of the final novel ingredient. The applicant provided additional information relating to the fumigation process, which includes the use of methyl bromide or aluminium phosphide, both of which form gases and do not leave residues. Fumigation is only carried out where necessary according to the production process flow-chart, and the applicant provided an SOP of the process as carried out by a contract company, along with a test certificate for methyl bromide residue.

III. History of the organism used as the source of the novel food

While there is a history of safe use for food ingredients derived from *Plantago ovata* in a number of countries, PSH is used within the EU only in food supplements for the relief of constipation or irregular bowel movement. In addition, some EU Member States class these products as medicines. Therefore, there is no history of consumption of PSH as a general food ingredient within the EU.

IV. – VIII. Sections relating to GMOs are not applicable

IX. Anticipated intake/extent of use of the novel food

The applicant intends to add PSH to breakfast cereals and cereal bars to a final level of 3.5g per serving. Using food consumption data generated by the Food Standards Agency in the UK the applicant predicts that, in a “worst case scenario”, between 57% and 80% of the adult population groups and 90% of 4 - 10 year old children would be possible consumers of PSH at some level. Teenage and adult males would have the greatest intake of PSH at a mean of 4.9g and 4.8 g/person/day respectively but the highest intake relative to bodyweight was estimated for children at 0.13g/kg body weight/day. PSH intake would result primarily from the consumption of breakfast cereals rather than cereal bars.

Cereal-based foodstuffs containing PSH, produced by Kellogg have had an estimated market penetration of 3%, 0.5% and 0.2% in the Canada, Australia and USA respectively, which suggests that the “worst case scenario” intake levels presented by the applicant are unlikely to be realised in the EU by the inclusion of PSH in breakfast cereals and cereal bars.

The intake modelling studies, along with market penetration data for certain third countries indicate that there will be moderate levels of consumer exposure to PSH in the EU. The UK and Ireland are generally regarded to have the highest intake of breakfast cereals and related products in the EU and thus PSH intake could be proportionately lower for many other EU Member States. Because of the limited appeal of the target food products, the 3.5g of PSH per serving and the proposed allergy advisory label for sensitised individuals, it is reasonable to assume that consumers, including children, are unlikely to consume excessive levels of PSH.

X. Information from previous human exposure to the novel food or its source

PSH is not naturally present in the European diet. Food supplements containing PSH (Metamucil etc.) are available in the EU for the relief and/or treatment of constipation and irregular bowel movements at a recommended daily dosage of approximately 3.5 - 10g of PSH per day. The level of exposure of EU citizens to PSH through food supplements is not known. The applicant provided an additional reference to the US Select Committee on GRAS Substances in 1982 that claimed an estimated four

million people in the US were exposed to low levels of PSH for 20 years, with no associated adverse health consequences.

XI. Nutritional information on the novel food

PSH will be used to partially replace existing sources of dietary fibre, while also providing an additional source of fibre in the diet. A typical nutritional profile is provided in Table XI.1-1 of the application dossier and shows that PSH is a rich source of dietary fibre and carbohydrate, with no saturated fat and little total fat or protein content. The potential benefits of PSH include stool bulking and ease of laxation, cholesterol reduction, reduced risk of coronary heart disease, reduced glycaemic index, improved insulin sensitivity and greater satiety resulting in better weight control. There is potential for PSH to increase the turnover of bile acids and negatively affect the absorption of fat-soluble vitamins (vitamins A and E) either by greater excretion of bile salts or the binding of fat-soluble vitamins by PSH. However, results from human and animal studies showed that such negative effects on fat-soluble vitamins were rarely significant. Negative effects on mineral absorption as a result of PSH consumption were found only when dietary intakes of those minerals were marginal.

XII. Microbiological information on the novel food

The microbiological data relating to this novel food is provided in the chemical and physical specification of PSH (Table I.5-1). Fumigation is a part of the production process only when pest or microbial loads are considered to be excessive and this was discussed in Section II. The company provided additional information on the microbiological criteria for PSH based on two or three class attribute plans, as appropriate, covering total aerobic mesophiles, yeasts, moulds, *E. coli, Salmonella, P. aeruginosa* and *S. aureus*. The microbiological analyses are carried out after the raw ingredient is imported from India to the US, and batch test results presented by the applicant in Table 1.6-1 of the application dossier are within acceptable limits. Further processing is carried out in the US which involves mechanical manipulation and the use of food-grade water and food-grade citric acid, none of which is expected to alter the microbial specifications once good hygiene and manufacturing practices are adhered to.

XIII. Toxicological information on the novel food

PSH is generally not absorbed from the gastrointestinal tract but is largely excreted unchanged. The mucilaginous and water-retaining properties of PSH result in more frequent bowel movements as well as an increase in faecal mass, bulk and total weight. Some reports suggest that up to 6% of ingested PSH can be hydrolysed in the stomach releasing *l*-arabinose, which can be absorbed and enter normal metabolic pathways. Further hydrolysis of PSH in the small or large intestines has not been reported, though intestinal bacterial fermentation to short chain fatty acids has been predicted on the basis of *in vitro* studies, along with *in vivo* studies in rodents and monkeys. However, the majority of human studies have provided only limited evidence of PSH fermentation in the bowel.

A range of toxicological studies in the early to mid 1900s showed that PSH is of low acute toxicity and is well-tolerated in subchronic and chronic studies carried out in a range of animal species. The development of pigmentation, observed within the epithelial cells in the collecting tubules of animal kidneys during feeding studies with *Psyllium* seed, was believed to be caused by the black-pigmented layer of the seed. This potential problem has been rectified by removing this seed layer during processing of PSH. More recent studies in rats and monkeys confirmed that PSH is well-tolerated, up to 10% dietary levels, though minor decreases in the absorption of certain nutrients, vitamins, and minerals were evident.

A range of clinical (therapeutic) studies involving daily doses of up to 30g of PSH demonstrated a good tolerance and evidence of possible health benefits including lowered serum total- and LDL-cholesterol in subjects with mild to moderate hypercholesterolemia. Side effects reported in a few of the trials included mild gastrointestinal symptoms such as flatulence, bloating and diarrhoea, all of which relate to high intakes of dietary fibre and which resolved at the end of the treatment.

A number of clinical studies on PSH have specifically been carried out on individuals suffering from irritable bowel syndrome (IBS). All the studies demonstrated that PSH consumption was well-tolerated up to six months, with only minor gastrointestinal side effects (*e.g.*, flatulence) reported. One clinical study has been reported where PSH was used as a dietary component rather than being administered

for therapeutic purposes (Metamucil etc.). PSH and wheat bran were administered in ready-to-eat cereals to 24 subjects for an 18 week period. Mild to moderate symptoms were reported in six out of the 18 subjects that consumed *Psyllium*, however, five subjects also reported the occurrence of gastrointestinal symptoms after consuming the wheat bran cereal.

Data specifically relating to reproductive toxicity, genotoxicity or carcinogenicity of PSH are not available. However, there were no indications of carcinogenicity in a series of studies lasting 5 months to lifetime durations undertaken to evaluate other endpoints. PSH has actually been shown to have a potential anti-cancer effect in several studies.

A number of reports linked oesophageal and gastrointestinal obstruction to the consumption of powdered PSH as a laxative. However, the primary cause was identified as a lack of proper hydration and possibly inappropriate use of the powdered product (*i.e.* not following the instructions correctly). Since being introduced to the US market, there have been no reports of gastrointestinal or oesophageal obstruction related to the consumption of cereals or cereal bars where the PSH is dispersed with other ingredients and, in the case of cereals consumed with milk.

Allergenicity

Allergic reactions to PSH have been reported in the earlier literature. The allergenic effect of PSH would appear to be primarily an occupational hazard as most of the reported cases occurred in sensitised people such as nurses, pharmaceutical plant workers and pharmacists previously exposed to PSH dust. Affected individuals developed anaphylaxis or other adverse reactions such as congestion, wheezing, etc. as a result of oral challenge with PSH-containing products, including cereals. However, there has been little evidence to suggest that allergic reactions could occur within the general population without prior sensitisation.

The allergen is primarily contained in the gum and protein fraction of the seed itself rather than within the husk. The potential for allergenicity among consumers has been largely controlled through the additional processing of PSH, resulting in an increase in its purity from 85% to 95%. In addition, a product label, proposed by the applicant, indicating that PSH may cause an allergic reaction in people sensitive to inhaled or ingested PSH powder should also be of benefit. These controls were factors in the virtual elimination of reported allergic reactions to cereal products containing PSH on sale in a number of third countries.

Conclusions

PSH continues to be used in third countries in general foodstuffs and in food supplement form in certain EU Member States, without any reports of significant health concerns. The information presented by Kellogg Company in the novel food application, along with subsequent clarifications, demonstrates that the use of PSH in breakfast cereals and cereal bars at the levels indicated should not pose a significant risk to the health of EU consumers. Specific labelling of cereals and cereal bars containing PSH to be implemented by the applicant should be sufficient warning to a small sub-group of consumers who may have been sensitised to PSH and at risk of an allergic reaction.

Though PSH is not listed in EU legislation for the purposes of allergen labelling, the advisory labelling to be undertaken by the applicant should follow the same criteria and be clear and legible on the packaging. The inclusion of PSH in breakfast cereals and cereal bars will be subject to general food legislation as well as specific EU legislation relating to the use of nutrition and health claims.

Recommendation

The FSAI is satisfied that the consumption of breakfast cereals and cereal bars containing PSH should not pose a significant risk to the health of EU consumers as long as the PSH is produced to the proposed specifications, is used in cereals and cereal bars only (3.5g PSH per serving) and with appropriate labelling to warn sensitised individuals.