Food Standards Agency
food.gov.uk

Mr Andreas Klepsch
European Commission
By Email

Reference
NFU 744

19 July 2010

Dear Mr Klepsch

INITIAL OPINION: MAGNOLIA BARK SUPERCRITICAL CARBON DIOXIDE EXTRACT AS A FOOD INGREDIENT.

Dear Mr Klepsch,

On 14 September 2009, the UK Competent Authority accepted an application from William Wrigley Jr. Company for Magnolia Bark Supercritical Carbon Dioxide Extract (MBSE) as a novel food ingredient, in accordance with Article 4 of Regulation (EC) 258/97. The Advisory Committee on Novel Foods and Processes (ACNFP) reviewed this application and their opinion is attached.

In view of the ACNFP's opinion, the UK Competent Authority considers MBSE, for use at a maximum level of 0.2% in chewing gum and mints meets the criteria for acceptance of a novel food, as set out in Article 3 (1) of Regulation 258/97.

Yours sincerely
(By email only)

Dr Manisha Upadhyay
For the UK Competent Authority

cc Marion Balz, William Wrigley Jr. Company
Nigel Baldwin, Cantox

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

OPINION ON AN APPLICATION UNDER THE NOVEL FOODS REGULATION FOR EXTRACT OF MAGNOLIA BARK

Applicant:	**William Wrigley Jr. Company**
Responsible Person:	**Marion Balz**
EC Classification:	**2.2**

Introduction

1. An application was submitted to the Food Standards Agency in September 2009 by William Wrigley Jr. Company for the authorisation of magnolia bark extract as a novel ingredient in the EU. A copy of the application was placed on the Agency's website for public consultation.

2. Magnolia bark extract is obtained from the bark of the plant *Magnolia officinalis*. This plant is native to the mountains and valleys of China and, according to the applicant, has been used for centuries as part of traditional Asian remedies. Magnolia bark supercritical carbon dioxide extract (MBSE) is mainly composed of two phenolic compounds, magnolol and honokiol. The applicant intends to incorporate MBSE into two confectionery products (chewing gum and mint confectionery products) at a maximum use level of 0.2% for breath freshening purposes.

3. The application for authorisation of magnolia bark extract was prepared pursuant to Commission Recommendation 97/618/EC of 29 July 1997 concerning the scientific aspects and presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients. Magnolia bark extract has been classified as a complex novel food from non-GM source, the source of the novel food has no history of food use in the EU (class 2.2).

I. Specification of the novel food

Information on this aspect is provided on p. 4-8 of the application dossier

4. The applicant states that MBSE contains two major 'active' components which comprise at least 94% of the product. The primary component is magnolol (5,5'-diallyl-2,2'dihydroxybipenyl) and the extract also contains smaller amounts of honokiol (5,3'-diallyl-2,4'-dihydroxybiphenyl). MBSE is a light brownish powder, soluble in alcohol and insoluble in water. The

specification for MBSE can be found in the table below.

Parameter	Specification
Appearance	Light Brownish Powder
Magnolol	92.5% min
Honokiol	0.5% min
Magnolol + Honokiol	94% min
Total Eudesmol	2% max
Moisture	0.5%
Impurities	
Arsenic (ppm)	0.5 max
Lead (ppm)	0.5 max
Total Heavy Metals (ppm)	10 max
Methyleugenol (ppm)	50 max
Turbocurarine (ppm)	2 max
Total Alkaloid (ppm)	100 max

***Discussion**: Members noted that compositional data from analyses of multiple batches of MBSE did not total 100% (range 95.7 -100.6%) and requested clarification of the identity of the remaining components. Members also requested confirmation of the absence of protein in MBSE and reassurance that quality control procedures are sufficiently robust to ensure product consistency. The applicant provided additional batch analyses data for fifteen lots of MBSE and stated that most of these batches are characterised to a consistently high purity of between 98 and 100%. The applicant also stated that individual batch analysis indicates that the majority of the product is accounted for by magnolol, honokiol and moisture content. At the Committee's request , the applicant analysed a sample of MBSE in duplicate for protein using three different methods (SDS-PAGE with Coomassie blue R250®, SDS-PAGE with silver staining and LC-MS/MS). The applicant stated that no detectable levels of protein were found in the MBSE analysed using any of the above methods. The Committee reviewed the raw data from these analyses and was reassured that protein is effectively absent from the novel ingredient.*

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

Information on this aspect is provided on p 9-12 of the application dossier

5. MBSE is obtained from the bark of *Magnolia officinalis* L, which is washed and oven dried to reduce moisture content before being crushed and extracted with supercritical carbon dioxide. The extract is dissolved in medical-grade ethanol and re-crystallised yielding MBSE.

6. MBSE is produced in accordance with Good Manufacturing Practice. The applicant states that a Hazard Analysis and Critical Control Point (HACCP) program has been implemented for the manufacture of MBSE.

7. The applicant carried out stability analyses of MBSE in chewing gum and mints over a 12 week period under accelerated storage conditions and concluded that the results demonstrate the stability of MBSE in chewing gum and mints, with minimal loss over the 12 week test period. At the request of the Committee, the applicant also provided real-time stability data for MBSE-containing gum (different flavours) over a ten month period. Magnolol content was assessed as a measure of stability and was shown to be stable within each flavour and there was no detectable degradation over 10 months of shelf-life.

***Discussion**: The Committee was satisfied with this section of the dossier and the additional data provided by the applicant.*

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

Information on this aspect is provided on p.13-15 of the application dossier

8. MBSE is obtained solely from the bark of *Magnolia officinalis* subsp. biloba. It is a species of Magnolia native to the mountains and valleys of China at altitudes of 300-1500m and it belongs to the family *Magnoliaceae*.

9. The applicant states that traditional herbal remedies containing magnolia bark, such as Banxia Houpo Tang, Saiboku-To, Hsiao-Cheng-Chi-Tang and Wuu-Ji-San, have been used for centuries as part of Asian remedies. The applicant also also states that various magnolia bark derived products are available, and these would all be regarded as traditional medicinal products. In view of this, the applicant sought clarification from the Medicines and Healthcare products Regulatory Agency (MHRA) on the medicinal status of MBSE and its proposed use in confectionery. The MHRA concluded that use of MBSE in chewing gum would not be medicinal, providing that it was limited to claims regarding breath freshening, and that the amount of MBSE did not exceed 3mg per stick. This limit is based on the potential medicinal function of the extract as an antibacterial agent and is not a safety limit.

***Discussion**: The Committee was generally content with this section of the dossier but requested an explanation for the rationale of incorporating 3 mg of MBSE into mint/gums. The applicant stated that a published study by Greenburg et al., 2007 reported that MBSE at a concentration of 0.2% displayed breath freshening properties and a 0.2% incorporation level was employed on this basis. Based on this use level and a maximum gum/mint size of 1.5 g each, each gum or mint serving would contain 3 mg of MBSE. The applicant also explains that there is also a technical limit on the use of MBSE in gum/mints because MBSE imparts unacceptable flavour characteristics to the product which are difficult to mask at incorporation levels above 0.2%. The Committee was satisfied with the applicant's response.*

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

Information on this aspect is provided on p 16-24 of the application dossier

10. The applicant intends to incorporate MBSE into gum and mints at a maximum level of 0.2%. Based on a maximum gum and mint size of 1.5g, each serving would contain up to 3mg of MBSE.

Proposed Food Use	Serving Size	MBSE (mg/serving)	Use-Level (%)
Mints	1.5g	3	0.2
Chewing Gum	1.4g	2.8	0.2

Summary of the individual proposed food-uses and use levels for MBSE in the UK

11. The applicant has indicated that MBSE will be added solely to mint and chewing gum products which are marketed for breath freshening purposes. MBSE will not therefore be added to bubble-gum type products or to other mint based confectionery such as 'Everton Mints'

12. The applicant has provided intake data from a range of population groups using information from the NDNS surveys which are available to the general public. On an absolute basis highest exposure to MBSE was observed in teenagers with 95th percentile estimates of 28 and 23 mg/person per day for gum and mints, respectively. On a mg/kg basis, exposure to MBSE in the diet was highest in children (age 4-11) at 0.6 and 1.04 mg/kg body weight per day for gum and mints, respectively.

Discussion*: The Committee was satisfied with this section of the dossier.*

X. Information from previous human exposure

Information on this aspect is provided on p.25 of the application dossier

13. The applicant does not view the limited use of magnolia bark products as traditional remedies to be indicative of widespread exposure to the principal components of MBSE. The applicant reports that MBSE has GRAS (Generally Recognised as Safe) status in the United States**.** MBSE-containing gum and mints have been marketed in US since June 2008 and Oct 2008, respectively. Post market monitoring for adverse reactions in the USA (2008-2009) indicated that there was one adverse report for every 11 million units sold.

14. As MBSE-containing gum and mints have been marketed in the US**,** the Committee requested details on the way in which these products are marketed. The applicant has provided details from Wrigley's US website to illustrate the way in which MBSE products are marketed in the US. While for

the EU application the applicant intends to limit claims to breath freshening properties, this appears not to be the case in the US where claims relating to antibacterial properties of the gums and mints are being made. Such claims would be illegal under EU legislation, as they would be regarded as medicinal.

***Discussion**: The Committee was satisfied with the applicant's response and did not raise any further questions/concerns on this aspect of the application.*

XI. Nutritional information on the novel food

Information on this aspect is provided on p.26 of the application dossier

15. The addition of MBSE to mints and gum is solely for the purposes of breath freshening and exposure to the novel ingredient is not expected to have a nutritional impact on the diet.

***Discussion**: The Committee did not raise any concerns or questions on this aspect of the application.*

XII. Microbiological information on the novel food

Information on this aspect is provided on p.7-8 of the application dossier

The applicant has provided microbiological analyses data for four different lots of MBSE which were shown to be demonstrably free from microbial contamination (*Clostridium*, coliforms, *Salmonella*, Staphylococci, mould and yeast).

***Discussion**: The Committee did not raise any concerns or questions on this aspect of the application.*

XIII. Toxicological information on the novel food

Information on this aspect is provided on p. 27-66 of the application dossier

Subchronic toxicity

16. The applicant conducted a 21 day toxicity study on MBSE in male and female Sprague-Dawley rats (Liu *et* al, 2007). This study was primarily a pilot dose-ranging study for a subsequent 90 day study. Animals consumed MBSE in the diet at doses of 0, 60, 120, 240 or 480 mg/kg body weight per day. Although differences in certain haematological parameters were observed, the applicant notes that these were of a low magnitude and were not dose responsive or consistent between sexes, and concludes that they are therefore not of biological relevance. Serum urea nitrogen and urine sodium values were significantly higher in the 120 mg/kg body weight/day females and males, respectively. Absolute and relative thyroid weights and relative kidney weights were slightly but significantly increased in females of the high

dose group. Relative spleen weight was slightly but significantly increased in males of the 60 mg/kg bodyweight/day group. The applicant states that organ weights were within the historical range of control weights and were not accompanied by clinical, gross or pathological effects, and therefore were not toxicologically relevant. The applicant states no treatment-related side effects were observed during this study. A NOAEL of 480 mg/kg body weight was determined (the highest dose administered).

17. The applicant also provides details of a 90 day study in which male and female Sprague Dawley rats consumed MBSE in the diet at doses of 0, 60, 120 or 240 mg/kg body weight per day. Although some differences in body weight, body weight gain and food consumption were observed, the applicant states that these effects were not dose related or toxicologically significant. Differences in certain haematological parameters (total bilirubin and sodium) were observed and urinalysis revealed significantly lower potassium levels in female animals dosed at 60 mg/kg body weight per day. The applicant states these differences were not dose dependent, not observed in both sexes and not biologically relevant. The applicant concludes that a NOAEL of 240mg/kg body weight was established.

Mutagenicity and genotoxicity

18. Ames tests conducted with and without metabolic activation were negative and MBSE was non-genotoxic in Chinese hamster ovary cells with and without metabolic activation. The applicant indicates that MBSE is non-genotoxic *in vivo* as no evidence of micronucleus induction was observed in Swiss Albino (CD-1) mice receiving MBSE doses up to 2,500 mg/kg body weight. The applicant considers that these studies indicate that MBSE is not mutagenic or genotoxic.

Human studies

19. The applicant has provided details of two double-blind human studies conducted to investigate the efficacy of MBSE. The results obtained from these studies indicated that consumption of MBSE-containing peppermint mints or gum was effective in reducing oral malodour. The applicant and the study investigator stated that the MBSE-containing products were well tolerated and that use/consumption of MBSE-containing mints did not result in any adverse effects in any of the study participants in either study. Headache was reported by one of the sixty two subjects in one of the studies, which the investigators judged was possibly related to the test product.

Toxicity studies and other studies conducted with magnolol, honokiol and crude magnolia bark preparations

20. Crude magnolia bark preparations have long been used as a component of traditional Asian remedies and the majority of published studies on the properties of magnolia bark have used the crude powdered bark or extracts produced using various solvent extraction processes. The applicant acknowledges that the test articles used in these studies are not representative of MBSE, and states that the available literature on these materials has been reviewed for completeness. This review includes a reference to mortality in animals fed 'large doses' of Houpo, a decoction (water extract) of magnolia bark that is produced for muscle relaxing purposes. The applicant notes that although the composition of this decoction is poorly defined, the findings are likely to be due to the presence of a water extracted alkaloid magnocurarine, which may have been present at concentrated levels in the extract.

21. Available data from acute and short-term animal toxicity studies carried out using these magnolia bark preparations are summarised below:

Species/Strain/No. of Animals per Group per Sex	Study Duration	Route	Dose Levels and Test Item (mg/kg body weight/day)	Observations	Reference
Mice					
Male ICR	Single dose	Gavage & i.p.	Ethanolic extract of Magnolia bark extract	Oral LD_{50} > 50 g/kg bw i.p $L.D_{50}$ = 8.5 g/kg bw	Yang and Chen, 1997
*NS	Single dose	Gavage	Houpo 60 g/kg bw	No fatalities	Murakami *et al.*, 1933
*NS	Single dose	i.p.	Houpo deconcoction	i.p. LD_{50} = 6.12 g/kg bw	Basic Medical Sciences Department, 1973
Rats					
Sprague-Dawley Male (200-250g) N=8-15/group	14 day	Gavage	- Houpo dried powder 5 g/kg bw - Houpo aqueous suspension for higher dose 10 g/kg bw	- No effect on behaviour, food/water intake or, body weight. - ↓ ALA, and Creatine - ↑ BUN - ↑ urine protein	Yang and Chen, 1997
Rabbits					
*NS	Single dose	i.v.	n/a	No Mortality	Chang and But, 1986
Dogs					
*NS	Single dose	i.v.	Houpo 1 g/kg	No mortality	Chang and But, 1986
Cats					
*NS	Single dose	i.v.	Houpo deconcoction	Minimum Lethal Dose (MLD) = 4.25 mg/kg bw	Basic Medical Sciences Department, 1973

*NS = Not Stated

The applicant acknowledges that various magnolia bark preparations or components thereof are reported in the literature as having claimed therapeutic effects and reported clinical actions including: anxiolytic and central depressant activity, muscle relaxation, vasorelaxation, thermoregulatory and antipyretic effects and protective properties on gastrointestinal mucosal membranes. The applicant also describes studies showing that magnolol and honokiol (the principal components of MBSE) may have beneficial effects on gastrointestinal function. The application dossier suggests that exposure to magnolol and honokiol resulting from the use of MBSE-containing gum and mints is limited and therefore effects on gastrointestinal function in humans are not expected.

In order to assess the validity of this conclusion, the Committee asked the applicant to provide data comparing levels of these compounds in the GI tract in the published studies and following exposure to MBSE from confectionery. The applicant reported that the observations described in the dossier were obtained from an uncontrolled study (Oikawa *et al*., 2005) on a herbal concoction containing many ingredients, one of which was a crude magnolia bark preparation.

As such the applicant advised that there is no credible clinical evidence to support any pharmacological effects of magnolol and honokiol on the GI tract. The applicant's response also highlighted that no GI effects were seen in the 90 day toxicity study where rats were administered MBSE in the diet at doses around 500 times higher that the estimated intake for frequent MBSE product users. The applicant's response also highlighted that post-market monitoring data also supported the lack of any pharmacological activity of MBSE.

The applicant also stated that the other studies mentioned above are for completeness and are not considered relevant to the proposed use of MBSE in gums and mints.

The Committee was satisfied that the applicant's response addressed its concerns on this point.

22. The applicant has also detailed a number of clinical trials investigating the use of Asian herbal remedies containing magnolia bark preparations that are not necessarily representative of MBSE. The applicant states that these studies suggest that the herbal preparations are well tolerated, although only one of these studies (Garrison and Chambliss, 2006) evaluated safety using clinical and haematology endpoints. In the study by Kelman *et al.,* 2008, one of forty two subjects reported side-effects which included heartburn, hands shaking and thyroid dysfunction. However, the applicant considers that these effects were not significant test-article-related effects. Similar side effects were also reported for one of forty two subjects in the study of Garrison and Chambliss, 2006, although these authors concluded that the treatment was well tolerated. These studies are summarised below and detailed in the dossier (p50-60).

Component	Source	Species	Route of Administration	Duration	Dose (mg/kg body weight)	Effect	Reference
Magnolol	Dietary supplement (Saiboku to) containing amongst other ingredients, magnolol	Human	Not reported	104 weeks	2.5 g Saiboku to 3 times daily (after meals); equivalent to 3.15 mg magnolol daily	Decrease in frequency of corticosteroid administration in responding bronchial asthmatics. No reduction in the frequency of corticosteroid administration among the non-responding subjects was reported. 'Responders' to Saiboku-To treatment exhibited higher free magnolol excretion rates than non-responders.	Homma *et al.*, 1993a
Extract of *M. officinalis*	Dietary supplement containing amongst other ingredients, *M. officinalis*	Human	Oral	3 times a day for 6 weeks	250 mg of supplement (amount of extract of *M. officinalis* not reported)	Well tolerated. Significant weight gain for placebo group but no weight gain for treatment group. (tested in overweight females age 20 to 50)	Garrison and Chambliss, 2006; Kalman *et al.*, 2006.
Magnoliae cortex bark	Dietary supplement Hange-koboku-to which also contained *Hoelen, Perillae herba* and *Zingiberis rhizoma*	Human	Oral	10 days	60 (of supplement)	Decrease in frequency of choking episodes caused by sleep apnoea	Hisanaga *et al.*, 2002.
Magnolia bark	Dietary supplement Hange-koboku-to which also contained *Hoelen, Perillae herba* and *Zingiberis rhizoma*	Human	Oral	4 weeks for patient 1, 6 months for patient 2 and 2 years for patient 3	7.5 g of supplement/day	No effect in patient 1, a 59-year-old women suffering from a panic disorder and agoraphobia. Patient 2: symptoms of agoraphobia disappeared after 12 weeks treatment, no return of symptoms 2.5 years after discontinuation of supplement. Patient 3: relief of panic disorder and agoraphobia after 2 weeks treatment. Attempted discontinuation caused return of symptoms so treatments was continued.	Mantani *et al.*, 2002.

Component	Source	Species	Route of Administration	Duration	Dose (mg/kg body weight)	Effect	Reference
Magnoliae cortex	Supplement Hange-koboku-to which also contained *Hoelen, Perillae herba* and *Zingiberis rhizoma*	Human	Oral	2 weeks	7.5 g of supplement/day	Gastric emptying rate increased in healthy volunteers but after a 2-week washout returned to normal. Gastric emptying rate increased in functional dyspepsia patients and a decrease in scores for abdominal pain, indigestion and constipation but not reflux or diarrhoea.	Oikawa *et al.*, 2005.
-	Banxia Houpo tang, which contains among other ingredients magnolia	-	Oral	4 weeks	4.5 g/day of herbal medicine	Decreased cough threshold in patients with aspiration pneumonia.	Iwasaki *et al.*, 2002
Extract of *M. officinalis*	Proprietary blend of patented extracts of the bark of *M. officinalis* (1.5% honokiol/capsule) and *Phellodendrom amurense* (0.1% berberine/capsule)	Human	Oral	6 weeks	750 mg of Relora® per day (approximately 11.25 mg/day of extract of *M. officinalis* was consumed)	Relora® reduced self-perceived stress and anxiety as well as temporary, transitory anxiety. No treatment-related safety concerns or significant adverse events were reported.	Kalman *et al.*, 2008

Safety of other phenolic and alkaloid constituents

23. In addition to the two biphenol compounds, magnolol and honokiol, magnolia bark provides essential oils containing alpha, beta and gamma-eudesmol. Magnolia barks contain small amounts of plant alkaloids (magnocurarine and tubocurarine) and methyleugenol. MBSE is produced using supercritical carbon dioxide chemical extraction so that the content of essential oils and contaminants is significantly reduced.

24. The applicant states that although beta-eudesmol has been reported to display antihypertensive effects in rats, such effects required intravenous or intraperitoneal doses of at least 10 or 30 mg/kg body weight respectively and no effects were observed at lower doses. The applicant's view is that, as MBSE is intended for food use, these observations are not relevant to the current evaluation. The applicant remarks that beta-eudesmol has also been

reported to have curare like action in rodents but these findings were not consistent in the literature. The specification for MBSE limits the total eudesmol content to 2% and the applicant highlights that MBSE intake from mints and gum would be several thousand to a million fold lower than doses reported to elicit significant biological effects and would therefore not be a safety concern.

25. The applicant states that several batches of MBSE were analysed for levels of methyleugenol, noting that a 20 ppm limit of this compound that has recently been set in EU flavourings legislation for its presence ready to eat savoury products[1]. The applicant estimates that, based on the proposed consumption of MBSE in gum and mints, 90th percentile intakes in the highest consumers (teenagers) would result in daily exposures of 375 ng/person and would not appreciably increase the dietary intake of this compound relative to background exposure from food (17 micrograms to 18,000 micrograms/person).

26. Given the very low concentration of curine alkaloids magnocurarine and tubocurarine that are expected to be present in the extract (the specifications limit alkaloids to a maximum of 100 ppm) and the fact that these compounds are poorly absorbed, the applicant concludes that these compounds will not be of toxicological concern as a result of consuming MBSE in mints and gum.

***Discussion**: The Committee sought an explanation for the gender-specific statistically significant increases in total blood bilirubin levels (TBBL) observed during the 90 day rodent feeding study. Noting that these increases were apparently not accompanied by other signs of liver toxicity, the Committee requested a copy of the original study report in order to be satisfied about this finding. The Committee reviewed this report and was satisfied that the 90 day report contained all relevant data and that the observed increases in TBBL were not dose-related. The Committee concluded that TBBL levels in the treatment group were significantly higher because TBBL levels in the control group were aberrantly low rather than as a result of any treatment-related effect.*

The Committee also requested further information on the metabolism of magnolol in the liver and reassurance as to whether there may be a risk of interaction with other pharmaceutical products metabolised in the liver.

The applicant states that the principal constituents of MBSE, magnolol and honokiol, are primarily metabolised by the liver in rodents via conjugation with

[1] The flavourings legislation defines limits for a range of food types to which flavourings containing methyleugenol might be added. This list does not include chewing gum or other confectionery and "ready to eat savoury products" is probably the closest surrogate for comparison.

glucuronic acid and the main elimination route is excretion in the bile. The applicant also states that there is limited information on the metabolism of magnolol and honokiol in humans, but based on available evidence glucuronidation appears to be the main metabolic route. The applicant states that a complete absorption, distribution, metabolism, excretion (ADME) profile of magnolol in humans is not available and neither are detailed metabolic data for honokiol (although given the structural similarity to magnolol the compound is expected to be metabolised similarly via conjugation of the free hydroxyl group with glucuronic acid and subsequently excreted in the bile).

The maximum level of MBSE consumption is a fraction of the exposure to other natural dietary components that undergo similar metabolic conjugation processes e.g. polyphenols which are found in chocolate, red wine, coffee, tea and many fruits and vegetables. The applicant considers that potential adverse drug interactions with MBSE and pharmaceuticals will be extremely unlikely. The Committee was satisfied with the information provided by the applicant relating to magnolol metabolism and potential interaction with pharmaceutical products.

XIV. Allergenicity and labelling

Information on this aspect is provided on p.25 of the application dossier

27. The applicant has indicated that the product will be labelled as appropriate and in accordance with EU legislation relating to the labelling presentation and advertising of foodstuffs. Claims will be limited to its breath freshening capability and that products containing MBSE will not have any medicinal or associated health or nutrition claims.

28. The applicant states that as MBSE is isolated using supercritical carbon dioxide extraction, it does not contain protein and therefore allergy concerns are not warranted.

***Discussion**: As noted above, the applicant provided data from additional protein analyses to support their statement that MBSE does not contain measurable amounts of protein and as such it is unlikely to pose a concern with respect to allergenicity. The Committee was satisfied with the applicant's response to this point.*

CONCLUSION

The Committee has reviewed the dossier and the additional information it requested from the applicant on a number of areas:

- Improved protein analyses
- Clarification of MBSE compositional data

- Gender-specific increases in total blood bilirubin levels observed during the 90 day rodent feeding study.
- Information on the metabolism of magnolol in the liver
- Information on the shelf-life of MBSE
- Details on how MBSE products are marketed in the US
- Further information on MBSE use levels.
- Information on ecology relating to the bark stripping process of magnolia trees.

The Committee was satisfied with the information provided by the applicant in addressing all its questions or concerns and was satisfied that MBSE for use in gums and mints at the specified use level of 0.2% is unlikely to pose a risk for consumers.

July 2010