ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

DRAFT OPINION ON AN APPLICATION UNDER THE NOVEL FOODS REGULATION FOR METHYLCELLULOSE

Applicant:	**Dow Wolff Cellulosics**
Responsible Person:	**Helen Stubbs**
EC Classification:	**2.2**

Introduction

1. An application was accepted by the Food Standards Agency in April 2012 from Dow Wolff Cellulosics for the authorisation of methylcellulose (MC) as a novel ingredient in the EU. A copy of the application was placed on the Agency's website for public consultation.

2. The applicant's MC has the polymeric backbone of cellulose, a natural carbohydrate obtained from plant material that contains a basic repeating structure of anhydroglucose units joined by 1-4 linkages. Each anhydroglucose unit contains hydroxyl groups at the 2,3 and 6 positions. Substitution of these hydroxyl groups creates a range of cellulose derivatives e.g. treatment of cellulosic fibres with caustic solution followed by a methylating agent yields methyl cellulose.

3. MC is currently approved as a food additive (E461) in the EU, functioning as an emulsifier, stabiliser or thickener. E461 is authorised for use in a range of foodstuffs at levels up to 0.5%. It was last evaluated in the EU in 1994, when the Scientific Committee on Food confirmed the JECFA allocation of an ADI "not specified" to a group of modified celluloses.

4. The applicant manufactures different grades of MC that gel at different temperatures; all fall within the range specified in the purity criteria for MC that accompany the food additive authorisation. Variation in the distribution of the polymer backbone, different positions of methyl groups within the glucose units and differences in molecular weight can all have an impact on gelling temperature so MC can gel in water at a temperature as low as 31°C or as high as 60°C.

5. The applicant is now proposing to market MC as a novel food ingredient in the EU, as a source of dietary fibre. MC is proposed to be added to a limited range

of foodstuffs (ice-cream, flavoured milk drinks, cold desserts, smoothie type drinks, yogurts and yogurt drinks and wet soups).

6. As MC does not have a significant history of consumption as a food ingredient in the EU, it requires a pre-market safety assessment and approval under the Novel Foods Regulation.

7. MC has been classified as a complex novel food from non-GM source, the source of the novel food has a history of food use in the EU (class 2.2) according to the scheme in Commission Recommendation 97/618 (EC).

Specification of the novel food

Information on this aspect is provided on p. 9-13 of the application dossier

8. The specification for MC can be found in the application dossier (p 13) and includes minimum purity, viscosity, moisture content and maximum limits for heavy metals. This specification matches that for the approved food additive E461 and encompasses a broad range of molecular weights from 20,000 to 380,000

9. The methyl cellulose products to be offered will encompass a range of different gelling temperatures and viscosities. Customer selection of particular product grades is expected to be food product-dependent, since food matrices can often impact the gelation properties of methyl cellulose (e.g. sugars lower the gelation temperature). Since viscosity is an important factor for mouth-feel and other food properties, a range of methyl cellulose products of differing viscosities will be offered to provide the best property options to food formulators.

10. The applicant has carried out analyses of nine independent lots of MC (p 13 of dossier) with a range of viscosities and in all cases MC meets the specifications.

***Discussion**: The Committee did not raise any concerns relating to this section of the dossier.*

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

Information on this aspect is provided on p 13-17 of the application dossier (CONFIDENTIAL)

11. The applicant has provided details in the dossier of the production processes for the manufacture of MC with a gelling temperature of 50-60˚C and for MC that gels as low as 31˚C. The applicant indicates that the same production processes are currently used to manufacture the approved food additive.

12. MC is manufactured by grinding wood pulp, followed by treatment with alkaline solution and methyl chloride, purification, drying and packaging. Reaction steps and times vary depending on the desired gelling properties of the end product. Further details are provided in the dossier.

13. MC products which gel at different temperatures have the same average content of methyl groups but differ in the position of these groups within the glucose units. MC that gels at 31°C is prepared by changing the reaction kinetics to favour methylation in positions 2 and 6 and to disfavour position 3. The position of the methyl groups alters the interaction of the glucose units within the polymer chain and also between the polymer chains, so that gelling can be obtained at body temperature (or lower) in a controlled way.

***Discussion**: The Committee did not raise any concerns relating to this section of the dossier.*

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

Annex 1, p 18

14. The applicant's MC is derived from highly purified cellulose from non-genetically modified plants e.g. softwood trees which are cultivated in a sustainable way. The same source material is also used to manufacture the approved MC food additive.

***Discussion**: The Committee did not raise any concerns relating to this section of the dossier.*

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

Information on this aspect is provided on p 19-24 of the application dossier

15. MC is proposed for use primarily in cold, wet, medium viscosity foods such as ice-cream, flavoured milk drinks, cold desserts, smoothie-type beverages, yoghurts, yoghurt drinks and cold soups with an anticipated use level of between 1.5 and 2%.

16. The applicant has used four cross-sectional food consumption surveys in the UK and Irish Republic to estimate potential exposure to MC. The applicant has provided estimates for different age groups (ages 1.5 to 64).

17. Using a deterministic approach, assuming all foods contain a fixed concentration of the maximum 2% MC, the highest overall predicted intake (97.5^{th} percentile) was for Irish male teenagers (4973±396 mg/day). When expressed on a body weight basis, the highest estimated intakes were for British female toddlers (326±29 mg/kg body weight/day).

18. The applicant has also provided estimates of current MC intake resulting from its existing permitted use as a food additive. The highest estimated baseline intake of MC as a food additive (97.5th percentile; assuming a highest fixed concentration for additive use of 0.5%) using a deterministic approach was observed for Irish adult males (2334±71 mg/day) when expressed as absolute intakes. On a body weight basis, highest intakes were observed for British female toddlers (70±2 mg/kg body weight/day).

19. The applicant notes that this approach is considered to be very conservative and yields "worst case" estimates; the estimates assume that MC is always present at a maximum fixed concentration in all foods and that all foods are consumed in high amounts by the same individuals.

20. The applicant has also used a probabilistic approach to estimate intakes of MC, taking variability in the concentration of MC into account while still assuming 100% probability that MC is present in all relevant foods.

21. Using this approach, the highest predicted intakes of MC as a novel ingredient (4273±322 mg/day and 282±26 mg/kg bodyweight/day) and highest baseline intakes as a food additive (1380±44 mg/day and 42±2 mg/kg bodyweight per day) are considered by the applicant to be more plausible than those obtained using a deterministic approach.

***Discussion**: The Committee did not raise any concerns with this section of the dossier.*

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

Information on this aspect is provided on p 28 of the application dossier

22. As previously stated, MC is an approved food additive (E461) in the EU and has been consumed since the mid 1950s.

***Discussion**: The Committee did not raise any issues with this section of the dossier.*

XI. Nutritional information on the novel food

Information on this aspect is provided on p 28 of the application dossier

23. The applicant states that as a food ingredient, MC fits under the 2nd category of material constituting dietary fibre, as defined in Annex II of Directive 90/496/EEC on nutrition labelling:

> "edible carbohydrate polymers which have been obtained from food raw material by physical, enzymatic or chemical means and which have a beneficial effect demonstrated by generally accepted scientific evidence";

24. The intended use of MC is as an additional source of dietary fibre and MC is not intended to replace any foodstuff in the diet.

25. The applicant outlines a study of vitamin uptake in the gut of rats, which indicated that MC did not interfere with vitamin uptake (vitamin A and thiamine).

Discussion: In the original dossier, the applicant stated that MC was intended to be used as a dietary fibre to promote satiety. The Committee was not convinced that MC can function to improve satiety and could see no evidence for this from the data in the dossier (there is no evidence of reduced food consumption in the animal studies). The applicant has clarified that it is seeking approval to market MC only as a dietary fibre at present and wishes to withdraw its references to promoting satiety.

In the dossier, the applicant referred to MC as being resistant to fermentation and reducing gastrointestinal distress. The Committee noted that the fermentability of native cellulose in the human large intestine ranges from <6% (for highly crystalline purified cellulose) to around 70% for more amorphous cellulose and requested information about where MC would fall within this range. The applicant admitted that the original sentence in the dossier could have been worded in a better way and should have read "Unlike many other dietary fibres, methyl cellulose (as well as other cellulose ethers) is resistant to fermentation in the colon. Therefore, replacing other dietary fibres with methyl cellulose will help to reduce overall fermentation and subsequent gastrointestinal distress." The Committee was satisfied with the applicant's responses relating to these points. The applicant has also referred the Committee to two studies in the dossier which show that MC passes through both animals and humans essentially unchanged and supports the idea that MC is not broken down by fermentation or absorbed.

During the 21 day public consultation, a comment was received noting that many patients with diarrhoea-predominant irritable bowel syndrome (IBS) need to avoid foods containing additives with a laxative effect. The Committee agreed that, while some consumers might regard a mild laxative effect to be beneficial, this effect would be undesirable in others such as those with IBS.

The Committee noted that consumption of foods with added fibre and fibre-like ingredients by children could result in an increase in common intestinal symptoms. The Committee advised therefore that foods containing MC should not be intended for children.

XII. Microbiological information on the novel food

Information on this aspect is provided on p.30 of the application dossier

26. The applicant states that MC is produced without the aid of microbiological processes and therefore no microorganisms or their metabolites are

anticipated. The production process of MC is strictly monitored and controlled and a HACCP hygiene procedure is followed.

27. The applicant has provided microbiological specifications for MC, taking into account a range of possible contaminating microorganisms. Analyses of four separate batches of MC showed that all batches comply with these specifications.

***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. 32-48 of the application dossier

28. The applicant reports a range of toxicological studies conducted with MC, as well as studies using other modified celluloses that may be regarded as analogues of MC.

Pharmacokinetics and metabolism

29. The applicant describes three feeding studies, one in humans and two studies using radio-labelled MC in rats (single dose and for five days), all of which demonstrate that essentially all orally administered MC is unabsorbed and is cleared through the body via the faeces.

Sub-chronic toxicity

30. The applicant presents five feeding studies investigating sub-chronic toxicity in rats and dogs. MC of various viscosities was incorporated into the diets of rats at up to 10% for time periods up to eight months and very few significant abnormalities or treatment related effects were reported. One study where different viscosities of MC (10cP or 4000 cP) were incorporated into the diets of rats at up to 10% for 90 days showed that male rats consuming 10% MC (low viscosity, 10cP) exhibited slight reductions in terminal body weight relative to controls but growth was normal in all other 10cP treatment groups and in groups consuming high viscosity MC (4000cP). No other significant treatment-related effects were observed in this study.

31. Rats fed a diet of 5% MC for thirty two weeks showed no change in dietary intake, growth, reproduction or tissue morphology. A subsequent experiment where the diet was supplemented with 50% MC significantly depressed growth due to lack of nutrient intake; this effect was diminished when rats were returned to a standard diet.

32. The applicant also briefly mentions a study where dogs (sex and strain not mentioned) were given up to 100g MC daily for four weeks and no adverse effects were reported.

Chronic/carcinogenicity studies

33. The applicant presents 2 two year rat feeding studies where rats were fed diets containing up to 0.1 or 5% MC of viscosity 15, 400 or 4000 cP. No treatment related effects (including mortality or increased tumour incidence) were reported (McCollister *et al*, 1973).

Genotoxicity

34. Results from two *in vitro* bacterial reverse mutation assays using *Salmonella typhimurium* strains (with and without metabolic activation) and an *in vitro* chromosome aberration test using a Chinese hamster lung fibroblast cell line showed that MC is not genotoxic.

Reproductive and developmental toxicity

35. Several animal feeding studies have investigated reproductive and developmental toxicity. For some of the studies, side effects were observed at the highest doses tested (1600 mg/kg bw/day rats; 685 mg/kg bw/day rabbits), which the applicant reports as secondary effects due to nutritional imbalance in the dams given a very high fibre diet. Effects included significant mortality and a decrease in pregnancy rates. In one rat feeding study, extra centres of ossification in the vertebrae were observed in the high dose group (1200 mg/kg bw/day).

Human studies

36. The applicant has described several human studies investigating the effects of MC on constipation and on lowering cholesterol. While there are reports of MC being effective in relieving constipation and increasing faecal bulk (independent of MC viscosity, according to the applicant), some of the studies do report GI effects such as bloating, flatulence and cramps. One of these studies did not employ a placebo comparator while another showed that these GI effects were comparable for the placebo group.

37. The applicant states that these human studies show that up to 6g MC, administered as a bolus dose, is well tolerated. The applicant suggests that the expected effects of MC on children and adults will be comparable to those experienced by an individual on a high fibre diet.

38. The highest predicted intakes of MC (97.5^{th} percentile) as a novel food ingredient using the deterministic approach are lower than 6g/day. However,

when baseline intakes of MC as a food additive are taken into account, it is possible that combined high level consumption may exceed 6g/day.

39. Using a probabilistic approach, which takes variability in the concentration of MC into account while still assuming 100% probability that MC is present in all relevant foods, the applicant calculates that the highest predicted intakes of MC as a novel food ingredient (97.5th percentile), combined with baseline intake, would not exceed 6g/day (see paragraph 21 above).

***Discussion**: The Committee did not raise any specific toxicological concerns relating to MC. The Committee did however question the relevance of the safety data relating to MC analogues that had been supplied in the dossier.*

The applicant has pointed out that the safety of methyl cellulose and other cellulose ethers (E 460 through to E 466) has been extensively evaluated as food additives (SCF, JECFA, EFSA, US FDA) and that in all these evaluations, a group approachwas usedbased on the similarity of their chemical structure and their toxicological and biochemical profiles, as demonstrated inanimal and human studies. The applicant acknowledges that some studies used to support the safety of cellulose ethers were not conducted recently ; however, each study has been extensively reviewed for information and validity. The applicant therefore feels it unnecessary to conduct further studies with MC.

The applicant has also emphasised that the manufacturing route for its low temperature gelling MC is consistent with that for other MC products. Therefore, the historic toxicity profiles for MC products are representative across all MC products, including lower temperature gelling MC.

The Committee was content with the applicant's responses to its questions. The Committee acknowledged, that although the studies presented in the dossier are relatively old, the lack of radio-label in tissues and urine is sufficient evidence that all of the alkyl celluloses pass through the gut essentially unchanged and no further studies were requested.

XIV. Allergenicity and labelling

Information on this aspect is provided on p.38 of the application dossier

40. The applicant states that MC is a substituted polysaccharide and therefore no proteins are expected to be present in the product. To verify the absence of proteins, samples of food grade MC (Methocel A4M) were analysed using the Antek total nitrogen chemiluminescence analyser for nitrogen as a presumptive test for protein. No nitrogen was detected (LOQ 1ppm). The applicant also highlights that there are no known intolerances to cellulosic products.

41. The applicant states that MC is intended to be labelled in the ingredients list as Methyl Cellulose.

42. The Committee's assessment focuses on safety and labelling, it does not address any nutrition or health benefits that may be claimed for the novel ingredient or for foods that contain it. Nutrition or health claims may only be made if they are specifically authorised under EU Regulation (EC) No 1924/2006.

***Discussion**: The Committee did not raise any concerns relating to this section of the dossier.*

CONCLUSION

The ACNFP has completed its assessment of MC as a novel ingredient to be added to a range of foods and did not have any safety concerns relating to this ingredient. The Committee did consider that the types of products to which MC is intended to be added may be particularly attractive to children which in turn may increase the potential for common intestinal symptoms in children. As with previous applications for similar novel ingredients, the Committee suggested that foods containing MC are not intended for children. The Committee raised questions relating to the extent to which MC is fermented in the human large intestine, the questionable role of MC in promoting satiety and the relevance of the applicant's safety data relating to MC analogues.
The applicant provided a response to clarify these points. The Committee was content that the applicant had addressed its questions in these areas.