Bureau Nieuwe Voedingsmiddelen
Novel Foods Unit

Methylcellulose

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. 2013-01 BNV, Utrecht, 29 maart 2013
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Beoordeling

Inleiding

Aan de orde is een tweede beoordeling volgens de Europese Verordening 258/97 (EG97), over het gebruik als nieuw voedingsmiddel van methylcellulose, een chemisch gemodificeerde vorm van cellulose, waarvoor houtpulp als bron wordt gebruikt. Het methylcellulose wordt geproduceerd door de firma Dow Wolff Cellulosics, en is bedoeld voor toepassing als ingrediënt in verschillende typen samengestelde voedingsmiddelen.

Het product werd bij de eerste beoordeling besproken als een nieuw voedingsmiddel in klasse 2.1: complexe nieuwe voedingsmiddelen uit een niet genetisch gemodificeerde bron, die binnen de EU al eerder voor de voeding is gebruikt (EG97a).

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 het Verenigd Koninkrijk door de *Advisory Committee on Novel Foods and Processes* (ACNFP). In het rapport van de eerste beoordeling concludeert de ACNFP dat methylcellulose veilig kan worden geconsumeerd bij het gebruik dat in het dossier wordt beschreven. Wel signaleert men dat inname van methylcellulose door kinderen zou kunnen bijdragen aan ongewenste darmeffecten. De ACNFP is dan ook van mening dat levensmiddelen met toegevoegd methylcellulose niet bedoeld zijn voor kinderen, maar constateert tevens dat de producttypen waaraan methylcellulose zal worden toegevoegd juist aantrekkelijk zijn voor kinderen.

Bevindingen van de Commissie VNV

De Commissie VNV heeft geen bezwaar tegen de toelating als nieuw voedingsmiddel van methylcellulose, maar maakt wel enkele kritische kanttekeningen bij de positieve eerste beoordeling door de ACNFP. Zo wordt volgens de commissie slechts summier ingegaan op eventuele ongewenste nutritionele effecten van een langdurige hoge inname van methylcellulose. Verder wijst de commissie er op dat producten met toegevoegd methylcellulose volgens de ACNFP niet voor kinderen bedoeld zouden moeten zijn, terwijl niet wordt besproken hoe een dergelijke beperking in de praktijk kan worden gerealiseerd. De commissie VNV heeft haar oordeel gebaseerd op de informatie in het dossier, waarvan de samenvatting is opgenomen als bijlage A, en de eerste beoordeling door de ACNFP, toegevoegd als bijlage B.

Productspecificatie. In de Engelse eerste beoordeling wordt vermeld dat de productspecificatie overeenkomt met de specificatie van methylcellulose, dat wordt gebruikt als voedseladditief (E461). In het dossier wordt een vergelijking gemaakt tussen de zuiverheidscriteria voor het additief E461 en de overeenkomstige gegevens voor het nieuwe voedingsmiddel. Daaruit blijkt dat beide beschrijvingen slechts op enkele details verschillen, die voor de veiligheidsbeoordeling geen gevolgen hebben. De productspecificatie staat variaties toe die resulteren in een verschillende geleertemperatuur en viscositeit. Het dossier

bevat analysegegevens voor negen verschillende productbatches met een uiteenlopende viscositeit.

Evenals de ACNFP ziet de commissie VNV in deze informatie geen reden voor bedenkingen.

Productieproces. De ACFP wijst er op dat het gebruikte productieproces overeenkomt met het productieproces voor het additief E461. In het dossier wordt vermeld dat bij de productie gebruik wordt gemaakt van een HACCP-programma.

De commissie VNV heeft geen vragen over dit onderdeel.

Informatie over de bron. De ACNFP vermeldt dat het methylcellulose wordt geproduceerd uit gezuiverd cellulose dat geïsoleerd is uit plantaardig materiaal, zoals houtpulp. Dit is vergelijkbaar met het uitgangsmateriaal voor het additief E461.

De commissie VNV heeft geen vragen over dit onderdeel.

Geschatte inname. De ACNFP benoemt het productassortiment, waaraan het methylcellulose zal worden toegevoegd, in een gehalte van 1,5 tot 2%. Daarbij gaat het om consumptie-ijs, melkdranken, desserts, *smoothies*, yoghurt en yoghurtdranken, en koude soepen. Vervolgens heeft de aanvrager voedselconsumptiegegevens gebruikt uit Ierland (voor de leeftijdsgroepen van 5-12 jaar; 13-17 jaar en 18-64 jaar) en het Verenigd Koninkrijk (voor de leeftijdsgroep van 1,5-4,5 jaar), om de inname van methylcellulose als ingrediënt bij deze toepassingen te schatten. De aanvrager heeft een deterministische benadering toegepast, waarbij is uitgegaan van gebruik van methylcellulose tot het maximale gehalte van 2% in alle voorgestelde categorieën voedingsmiddelen. Dat leidt tot een maximale geschatte inname van 4973 mg per dag voor jongens in de leeftijdsgroep van 13-17 jaar (97,5^{e} percentiel van de gebruikers). Op gewichtsbasis is de geschatte inname het hoogst voor meisjes van 1,5-4,5 jaar (326 mg/kg bw/d voor het 97.5^{e} percentiel van de gebruikers). Daarnaast is ook een innameschatting gemaakt voor het gebruik van methylcellulose als voedseladditief tot een maximaal gehalte van 0,5%. Daaruit volgt een hoogste inname voor mannen van 18-64 jaar (2334 mg/d voor het 97.5^{e} percentiel van de gebruikers), en op gewichtsbasis een hoogste inname voor meisjes van 1,5-4,5 jaar (70 mg/kg bw/d voor het 97,5^{e} percentiel van de gebruikers). De aanvrager is van mening dat een realistischer beeld ontstaat als een probabilistische benadering wordt gevolgd, waarbij rekening wordt gehouden met een veronderstelde variatie in de concentratie methylcellulose van 1,5-2,0% bij gebruik als ingrediënt en 0,1-0,5% bij gebruik als additief. De aanvrager schat de hoogste inname in dat geval op 4273 mg/d voor het beoogde gebruik als ingrediënt (jongens van 13-17 jaar, 97,5^{e} percentiel van de gebruikers) en op en op 1379 mg/d voor het gebruik als additief (mannen van 18-64 jaar, 97,5^{e} percentiel van de gebruikers). Op gewichtsbasis bedraagt de hoogste geschatte inname 283 mg/kg bw/d voor het gebruik als ingrediënt, en 42 mg/kg bw/d voor het gebruik als additief (in beide gevallen voor meisjes van 1,5-4,5 jaar, 97,5^{e} percentiel van de gebruikers).

De Commissie VNV constateert dat in de eerste beoordeling door de ACNFP alleen wordt ingegaan op cijfers voor hoge consumptie, waardoor voorbij wordt gegaan aan de spreiding binnen de onderzochte groepen. Uit de informatie in het dossier blijkt dat de schatting van de gemiddelde inname doorgaans ruim drie keer lager ligt dan de schatting van de inname voor het 97.5^{e} percentiel. De commissie VNV heeft geen principieel bezwaar tegen het gebruik van de in dit dossier gevolgde probabilistische methode.

Eerder gebruik. De ACNFP vermeldt dat methylcellulose al sinds de vijftiger jaren van de vorige eeuw wordt geconsumeerd.

De commissie VNV heeft geen vragen over dit onderdeel.

Voedingskundige informatie. De ACNFP beschrijft een discussie met de aanvrager over het lot van het methylcellulose in het lichaam, en neemt aan dat het product in principe de darm zal passeren, zonder te worden opgenomen of omgezet. De ACNFP wijst er ook op dat consumptie door kinderen van voedingsmiddelen met toegevoegde vezels en vezelachtige ingrediënten zou kunnen leiden tot een toename van maag-darm klachten. Volgens de ACNFP zijn voedingsmiddelen met toegevoegd methylcellulose daarom niet bedoeld voor kinderen. Verder concludeert de aanvrager in het dossier op grond van beperkte experimentele gegevens dat methylcellulose geen effect zou hebben op de opname van vitamines uit de darm.

De commissie VNV wijst er op dat in het dossier en in het rapport van de eerste beoordeling weinig aandacht wordt besteed aan mogelijke effecten van een langdurige inname van aanzienlijke hoeveelheden methylcellulose op de opname van microvoedingsstoffen in de darm. Ook merkt de commissie op dat de ACNFP geen consequenties verbindt aan haar constatering dat voedingsmiddelen met methylcellulose niet bedoeld zijn voor kinderen. Het beoogde productassortiment omvat juist categorieën die ook voor kinderen aantrekkelijk zullen zijn.

Microbiologische informatie. Volgens de ACNFP volstaan HACCP procedures in combinatie met de microbiologische specificatie die door de aanvrager wordt gehanteerd.

De commissie VNV heeft geen vragen over dit onderdeel.

Toxicologische informatie. Het dossier en de eerste beoordeling gaan uitgebreid in op een groot aantal experimentele gegevens in proefdieren, waarbij verschillende preparaten werden gebruikt van methylcellulose en van verwante chemisch gemodificeerde vormen van cellulose. Daarnaast worden in het dossier een aantal studies beschreven in de mens. De ACNFP stelt dat hieruit volgens de aanvrager blijkt dat een inname van methylcellulose van 6 g/d in één enkele dosis goed wordt verdragen. De ACNFP beschrijft dat zij over dit deel van het dossier nadere vragen heeft gesteld, en de reactie van de aanvrager hierop accepteert. De aanvrager heeft daarbij gewezen op de uitgebreide beoordelingen van methylcellulose door gezaghebbende internationale instanties, waarbij ook gegevens over verwante verbindingen zijn beschouwd. Zo oordeelde de *Joint FAO/WHO Expert Committee on Food Additives* (JECFA) dat het niet nodig was een ADI-waarde vast te stellen voor het gebruik van chemisch gemodificeerde vormen van cellulose als voedseladditief. De ACNFP accepteerde gegevens over de afwezigheid van eiwit in methylcellulose als argument dat methylcellulose geen allergene eigenschappen heeft.

De commissie VNV heeft geen vragen over dit onderdeel.

Conclusie

De commissie VNV stemt in met de eindconclusie van de ACNFP dat methylcellulose veilig kan worden gebruikt als ingrediënt in de voeding, zoals voorgesteld in het dossier. De commissie VNV merkt echter wel op dat in het dossier en in het rapport van de eerste beoordeling maar weinig aandacht wordt besteed aan eventuele voedingskundige effecten van een langdurige hoge inname van toegevoegd methylcellulose. Daarnaast vindt de commissie VNV het opmerkelijk dat de ACNFP constateert dat voedingsmiddelen met

methylcellulose niet bedoeld zijn voor kinderen, maar geen consequenties verbindt aan deze uitspraak. Volgens de commissie ligt het voor de hand om inname door kinderen te beperken door inperking van het productassortiment of door etikettering.

Referenties

EG97 Verordening (EG) nr. 258/97 van het Europees Parlement en de Raad van 27 januari 1997 betreffende nieuwe voedingsmiddelen en nieuwe voedselingrediënten. Publicatieblad van de Europese Gemeenschappen 1997; L43: 1-6.

EG97a Aanbeveling (EG) nr. 97/618/EG van de Commissie van 29 juli 1997 betreffende de wetenschappelijke aspecten en de presentatie van de informatie die nodig is om aanvragen voor het in de handel brengen van nieuwe voedingsmiddelen en nieuwe voedselingrediënten te ondersteunen alsmede het opstellen van de verslagen van de eerste beoordeling uit hoofde van Verordening (EG) nr. 258/97 van het Europees Parlement en de Raad. Publicatieblad van de Europese Gemeenschappen 1997; L253: 1-36.

Assessment

Introduction

This report describes a second assessment under European Regulation 258/97 (EC97) of the use as a novel food of methylcellulose: a chemically modified form of cellulose, for which wood pulp is used as the source. The methylcellulose is produced by a company called Dow Wolff Cellulosics, and is intended for use as an ingredient in various types of processed foods.

In the context of the initial assessment, the product was considered as a novel food in class 2.1: complex novel foods from a non-genetically modified source, with a history of food use in the EU (EC97a).

The second assessment reported here was performed by the Novel Foods Unit of the Medicines Evaluation Board, in accordance with the European authorization procedure. The Unit consulted the Committee on the Safety Assessment of Novel Foods (referred to below as 'the VNV Committee') regarding its assessment.

Initial assessment

The initial assessment of the application to place the novel food on the market was conducted in the United Kingdom by the Advisory Committee on Novel Foods and Processes (ACNFP). In the report on its initial assessment, the ACNFP concludes that methylcellulose can safely be consumed when used as described in the dossier. The ACNFP nevertheless states that the consumption of methylcellulose by children could contribute to an increase in intestinal symptoms. The ACNFP accordingly takes the view that foodstuffs with added methylcellulose should not be intended for children, while pointing out that the types of product to which methylcellulose is to be added are particularly attractive to children.

Findings of the VNV Committee

The VNV Committee does not object to methylcellulose being authorized for use as a novel food, but has a number of criticisms of the positive initial assessment by the ACNFP. For example, the Committee feels that relatively little consideration was given to the possibility of prolonged consumption of large amounts of methylcellulose having undesirable nutritional effects. The Committee also notes that, although the ACNFP is of the opinion that products with added methylcellulose should not be intended for children, the initial assessment does not indicate how the consumption of such products might be controlled in practice. The VNV Committee based its assessment on the information in the dossier, which is summarized in annex A, and the initial assessment by the ACNFP, which forms annex B.

Product specification. According to the information in the dossier and the initial assessment, the product specification corresponds to the specification of methylcellulose that is used as a food additive (E461). The dossier contains a comparison between the purity criteria for the additive E461 and the corresponding data for the novel food, demonstrating that the two definitions differ only in certain details, which are not relevant to the safety assessment. The product specification allows a degree of variation, resulting in a range of gelling temperatures and viscosities. The dossier contains analysis data for nine different product batches, varying in viscosity.

The VNV Committee agrees with the ACNFP's view that the information about the product specification gives no cause for concern.

Production process. The ACNFP indicates that the production process used corresponds to that used for the additive E461. The dossier states that production will be controlled using an HACCP programme.

The VNV Committee has no questions regarding this aspect.

Information about the source. The ACNFP reports that the methylcellulose is produced from purified cellulose derived from plant-based material, such as wood pulp. Such material is comparable to the starting material for the additive E461.

The VNV Committee has no questions regarding this aspect.

Estimated intake. The ACNFP lists the range of products, to which methylcellulose is to be added at a concentration of 1.5 to 2%. The products in question are ice-cream, flavoured milk drinks, cold desserts, smoothie-type drinks, yogurts and yogurt drinks, and cold soups. The applicant has then used food consumption data from Ireland (for the age groups 5 to 12 years, 13 to 17 years and 18 to 64 years) and from the UK (for the age group 1.5 to 4.5 years) to estimate what the intake of methylcellulose would be if it were used as an ingredient in the production of the said products. The applicant took a deterministic approach, assuming use of methylcellulose at the maximum concentration of 2% in all the proposed categories of food. On that basis, the applicant arrived at a maximum estimated intake of 4973 mg per day, in boys in the age group 13 to 17 years (97.5th user percentile). Relative to bodyweight, the estimated intake came out highest for girls aged 1.5 to 4.5 years (326 mg/kg bw/d for the 97.5th user percentile). Intake was also estimated assuming use of methylcellulose as food additive at a maximum concentration of 0.5%. The highest intake thus estimated was in men aged 18 to 64 years (2334 mg/d for the 97.5th user percentile), while the highest figure relative to bodyweight was again in girls aged 1.5 to 4.5 years (70 mg/kg bw/d for the 97.5th user percentile). The applicant believes that a more realistic picture is obtained using a probabilistic approach, assuming use of methylcellulose as an ingredient at a concentration varying between 1.5 and 2.0%, and assuming use of methylcellulose as an additive at a concentration varying between 0.1 and 0.5%. On that basis, the applicant estimates the highest level of intake to be 4273 mg/d when methylcellulose is used as an ingredient for the intended purposes (boys aged 13 to 17 years, 97.5th user percentile) and to be 1379 mg/d when methylcellulose is used as an additive (men aged 18 to 64 years, 97.5th user percentile). Relative to bodyweight, the highest estimated intake is then 283 mg/kg bw/d when methylcellulose is used as an ingredient, and 42 mg/kg bw when methylcellulose is used as an additive (in both cases, for girls aged 1.5 to 4.5 years, 97.5th user percentile).

The VNV Committee notes that the initial assessment by the ACNFP considers only the data on high level consumption, thus disregarding the distribution within the investigated groups. From the information in the dossier, it appears that the estimated average consumption is generally more than three times lower than the estimated consumption for the 97.5th percentile. The VNV Committee does not object in principle to the use of the probabilistic method underpinning the calculations in the dossier.

Previous use. The ACNFP reports that methylcellulose has been consumed since the 1950s.

The VNV Committee has no questions regarding this aspect.

Nutritional information. The ACNFP records an exchange with the applicant regarding the fate of methylcellulose in the body, and assumes that the product will in principle pass through the digestive system, without being absorbed or metabolized. The ACNFP also points out that consumption of foods with added fibre and fibre-like ingredients by children could lead to an increase in gastrointestinal symptoms. According to the ACNFP, foods with added methylcellulose should not therefore be intended for children. In the dossier, the applicant additionally concludes, on the basis of limited experimental data, that methylcellulose would not affect the absorption of vitamins from the digestive tract.

The VNV Committee points out that neither the dossier nor the report on the initial assessment pay very much attention to the possible effects of prolonged consumption of large amounts of methylcellulose on the absorption of micronutrients via the digestive tract. The Committee also notes that the ACNFP attaches no consequences to its observation that foods with methylcellulose should not be intended for children, although the range of products for which methylcellulose is intended includes products that may be particularly attractive to children.

Microbiological information. According to the ACNFP, the combination of the HACCP procedures and the microbiological specification used by the applicant are sufficient.

The VNV Committee has no questions regarding this aspect.

Toxicological information. The dossier and the initial assessment pay detailed attention to a large volume of data from experimental animal research, in which various preparations of methylcellulose and of related chemically modified forms of cellulose were used. The dossier also describes a number of studies in humans. The ACNFP states that, according to the applicant, the data show that the consumption of 6 g/d of methylcellulose in the form of a single daily dose is readily tolerated. The ACNFP records that it asked the applicant further questions about the part of the dossier containing that assertion, and accepted the applicant's response. The applicant drew attention to the extensive investigations of methylcellulose by authoritative international bodies, in which context data on related compounds had also been considered. So, for example, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) had concluded that it was not necessary to define an ADI value for the use of chemically modified forms of cellulose as food additives. The ACNFP accepted the data on the absence of protein from methylcellulose as evidence that methylcellulose had no allergenic properties.

The VNV Committee has no questions regarding this aspect.

Conclusion

The VNV Committee supports the ACNFP’s final conclusion that methylcellulose may safely be used as a food ingredient, as proposed in the dossier. However, the VNV Committee points out that neither the dossier nor the report on the initial assessment pay very much attention to the possible nutritional effects of prolonged consumption of large amounts of methylcellulose. The Committee also considers it remarkable that the ACNFP states that foods with methylcellulose should not be intended for children, yet attaches no consequences to that statement. The VNV Committee believes that the natural corollary of the conclusion that foods with methylcellulose should not be intended for children is that

consumption by children should be regulated by restricting the range of products in which methylcellulose is used, or by labelling.

References

EC97 Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients. Official Journal of the European Communities 1997; L43: 1-6.

EC97a 97/618/EC. 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 and the preparation of initial assessment reports under Regulation (EC) No 258/97 of the European Parliament of the Council. Official Journal of the European Communities 1997; L253: 1-36.

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A Samenvatting van het dossier / Summary of the dossier

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Methyl Cellulose Novel Food Dossier

Dossier submitted by Leatherhead in November 2011 on behalf of Dow Wolff Cellulosics, for evaluation pursuant to Regulation (EC) 258/97 (as amended) on novel foods and novel food ingredients by the UK Competent Authority on Novel Foods (UK Food Standards Agency).

SUMMARY

Introduction

The use of methyl cellulose for nutritional purposes rather than as an approved food additive (E 461) is a new development in the EU and therefore falls within the scope of the Novel Food Regulation (EC) No. 258/97. Dow Wolff Cellulosics (Dow) seeks approval for the novel use of methyl cellulose for nutritional purposes (source of dietary fibre) in a limited range of food categories within the framework of Article 1 (2) (e) of Regulation (EC) No. 258/97.

Proposed food uses are as follows: Ice-cream, milk beverages, puddings, smoothie-type beverages, yogurts, yogurt beverages and wet soups with a concentration of methyl cellulose up to 2%.

Anticipated Intake

Average daily intakes of methyl cellulose were estimated from four cross-sectional food consumption surveys in the UK and the Republic of Ireland using a deterministic and probabilistic approach. Anticipated use levels for methyl cellulose as a novel food ingredient were between 1.5 and 2.0 % and for methyl cellulose as a food additive between 0.1 and 0.5 %.

Deterministic approach (assuming 100% probability of presence of methyl cellulose in all food groups and a fixed maximum concentration)

Highest predicted intakes of methyl cellulose as a novel food ingredient (97.5th percentile ±SE; consumers only) are 4973±396 mg/day, 326±28.87 mg/kg bw/day.

Highest baseline intakes of methyl cellulose as a food additive (97.5th percentile ±SE; consumers only) are 2334±71 mg/day; 69.63±2.27 mg/kg bw/day.

Probabilistic approach (assuming 100% probability of presence of methyl cellulose in all food groups and variable concentration levels)

Highest predicted intakes of methyl cellulose as a novel food ingredient (97.5th percentile ±SE; consumers

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only) are 4273.3±322.5 mg/day; 282.54±25.77 mg/kg bw/day.
Highest baseline intakes of methyl cellulose as a food additive (97.5th percentile ±SE; consumers only) are 1379.2± 44.5 mg/day; 41.89±1.58 mg/kg bw/day. 5

Safety Studies

A review of toxicology data available for methyl cellulose and its analogues indicates that consumption of up to 6g per day of methyl cellulose is likely to be tolerated without adverse side effects (Snape, 1989).

Due to its physical nature, Dow's methyl cellulose is not believed to pose a significant choking or overdose hazard.

The effect on the human gut regarding gastrointestinal intolerance and laxation with increased consumption of methyl cellulose is expected to be similar to any individual consuming a high fibre diet.

Conclusion

Probabilistic intake estimates, which take variability in the concentration of methyl cellulose into account whilst still employing a conservative assumption of 100% probability of presence, are considered to be more plausible than deterministic intake estimates. Highest predicted intakes of methyl cellulose as a novel food ingredient using a probabilistic approach (97.5th percentile; consumers only) are lower than the lowest plausible safety threshold of 6g/day derived from a human study (Snape, 1989). When baseline (probabilistic) intakes of methyl cellulose as a food additive are taken into account, it is likely that combined high level intakes would still be lower than the plausible safety threshold of 6g/day.

On the basis of the available toxicological and safety data, and conservative intake estimates, the proposed extended use of methyl cellulose as a novel food ingredient is unlikely to pose a safety concern for humans.

B Eerste beoordeling / Initial assessment

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

OPINION ON AN APPLICATION UNDER THE NOVEL FOODS REGULATION FOR METHYLCELLULOSE

Applicant: **Dow Wolff Cellulosics**

Responsible Person:

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 19-27 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 (97.5^{th} 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 28-29 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.30-31 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 approach was used based on the similarity of their chemical structure and their toxicological and biochemical profiles, as demonstrated in animal 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.

October 2012