

# **METHYL CELLULOSE**

Dossier prepared with and submitted 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)

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## 1 EXECUTIVE 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 to increase satiety) in a limited range of food categories within the framework of Article 1 (2) (e) of Regulation (EC) No. 258/97. This application has been prepared in accordance with Commission Recommendation 97/618/EC concerning the scientific information and safety assessment report required for novel foods.

### Intended use

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 (97.5<sup>th</sup> percentile  $\pm$ SE; consumers only) are 4973 $\pm$ 396 mg/day, 326 $\pm$ 28.87 mg/kg bw/day.

Highest baseline intakes of methyl cellulose as a food additive (97.5<sup>th</sup> percentile  $\pm$ SE; consumers only) are 2334 $\pm$ 71 mg/day; 69.63 $\pm$ 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 (97.5<sup>th</sup> percentile  $\pm$ SE; consumers only) are 4273.3 $\pm$ 322.5 mg/day; 282.54 $\pm$ 25.77 mg/kg bw/day.

Highest baseline intakes of methyl cellulose as a food additive (97.5<sup>th</sup> percentile  $\pm$ SE; consumers only) are 1379.2 $\pm$  44.5 mg/day; 41.89 $\pm$ 1.58 mg/kg bw/day.

### **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) which is further detailed in Section 11.1.10.1 (p.47, 2<sup>nd</sup> paragraph).

Due to its physical nature, Dow's methyl cellulose is not believed to pose a significant choking or overdose hazard. Choking potential of the gel is further detailed in Section 11.2.1.

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. See section 11.2.3.

### **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 (97.5<sup>th</sup> 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.

## **2 ADMINISTRATIVE DETAILS**

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### 3 INTRODUCTION

Cellulose is a polymer forming the structural basis of the cell walls of plants. Dow Wolff Cellulosics (Dow) produces methyl cellulose using purified cellulose extracted from cellulose containing non-genetically modified plants such as trees (mainly softwood), which is then partially etherified with methyl groups. It belongs to a group of edible carbohydrate polymers, referring to compounds that are analogous to those of naturally-occurring dietary fibres. These compounds demonstrate the physiological properties of the respective materials for which they are analogous, but are not obtained by eating the whole part of the native originating plant (Tungland and Meyer, 2002).

Methyl cellulose is currently an approved food additive (E 461) in the European Union (EU) under Annex I of Directive 95/2/EC (as amended) (European Commission 1995) and which has been implemented in national legislation of all EU Member States. Dow is currently selling methyl cellulose in the EU as E 461 which is derived from the same material (softwood). Recommended usage levels to obtain a desired technological function range from 0.1 to 0.5%. The approval for marketing methyl cellulose in the EU only applies to its use for technological purposes in foodstuffs. It can be used at *quantum satis* as an emulsifier, stabiliser or thickener.

Dow's different grades of methyl cellulose which gel at different temperatures are hereafter referred to as methyl cellulose. All these methyl celluloses are the same substance as specified in the purity criteria for methyl cellulose as a food additive (E 461), only the distribution of the polymer backbone is different so methyl cellulose can gel *in vitro* in water at temperature as low as 31°C instead of 50°C for traditional methyl cellulose.

Dow is proposing to market its methyl cellulose as a novel food ingredient in the EU as a source of dietary fibre to increase satiety (see further details in section 9, last paragraph) in a limited range of foodstuffs such as ice-cream, flavoured milk drinks, cold desserts, smoothie-type beverages, yogurts, yogurt drinks and wet soups, at levels ranging from 1.5% to 2%. However, methyl cellulose does not have a significant history of consumption within the EU as a food ingredient before 15 May 1997. It would therefore be considered a novel food ingredient. According to the Novel Foods Regulation, it must be subject to a pre-market safety assessment before it can be authorised for the EU market.

Dow is therefore seeking approval under Novel Foods Regulation (EC) No 258/97.

Following a safety evaluation, the intent is to market methyl cellulose as a novel food ingredient under the Satisfit™ and METHOCEL™ trade name umbrella.

Methyl cellulose as a novel food ingredient would fall under the novel food category described under Article 1 (2) (e) of Regulation (EC) No. 258/97: 'foods and food ingredients consisting of or isolated from plants and food ingredients isolated from animals, except for foods and food ingredients obtained by traditional propagating or breeding practices and having a history of safe food use'.

This application has been prepared in accordance with Commission Recommendation 97/618/EC concerning the scientific information and safety assessment report required for novel foods (European Commission 1997). This Recommendation divides novel foods into six classes and requires specific safety information to be provided for each class by answering specific questions. Methyl cellulose would be classified under Class 2.2 "Complex Novel Food from non-GM source, the source of the Novel Food has no history of food use in the Community".

Commission Recommendation 97/618/EC requires specific safety questions to be answered for Class 2.2 novel foods under the topics as detailed below:

	<b>Related dossier section where answers to safety questions have been provided</b>
I Specification of the Novel Food	<b>4</b>
II Effect of the Production Process Applied to the Novel Food	<b>5</b>
III History of the Organism Used as the Source of the Novel Food	<b>6</b>
IX Anticipated Intake/Extent of Use of the Novel Food	<b>7</b>
X Information from Previous Human Exposure to the Novel Food or Its Source	<b>8</b>
XI Nutritional Information on the Novel Food	<b>9</b>
XII Microbiological Information on the Novel Food	<b>10</b>
XIII Toxicological Information on the Novel Food	<b>11</b>

Proposed labelling of the novel food ingredient is provided in section 12.

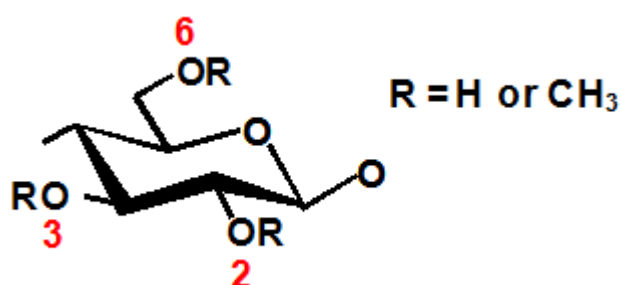


## 4 Specification of the Novel Food

### 4.1 General Description

Dow's food grade methyl cellulose has the polymeric backbone of cellulose, a natural carbohydrate that contains a basic repeating structure of anhydroglucose units (Figure 1). The number of anhydroglucose units can vary between approximately 100 and 2,000 depending, for example, on the cellulose raw material used.

**Figure 1 General Chemical Structure Formula of the Repeating Unit of Methyl Cellulose**



Cellulose has a polymeric backbone with a 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 hydroxyls creates cellulose derivatives. For example, treatment of cellulosic fibers with caustic solution, followed with a methylating agent, yields methyl cellulose. The fibrous reaction product is purified and ground to a fine uniform powder (for more details on production process see section 5 below).

One property of methyl cellulose is that it is known to exhibit reverse thermal gelation, in other words, methyl cellulose gels at warmer temperatures and forms a liquid again at cooler temperatures. Methyl cellulose can be designed to gel at temperatures of as low as 31°C and as high as 60°C. In the METHOCEL Cellulose Ethers Technical Handbook (Dow, 2002), methyl cellulose is shown that gels with *in vitro* gelling temperatures in water going as high as 50°C. Sarkar (Sarkar, N. 1979) reported on methyl cellulose that gels with *in vitro* gelling temperatures in water as high as 50°C. In the US Patent No. 6,235,893 a process is described to produce methyl cellulose that gels with *in vitro* gelling temperatures in water going as low as 31°C.

Dow's methyl cellulose which can gel at different temperatures complies with the criteria set of E 461. It retains the same average content of methyl groups (degree of substitution, DS) but the distribution of those groups within the glucose units is different. Methyl cellulose with gelation temperatures of as low as 31°C, and which still falls into E 461 criteria set, is prepared by changing the reaction kinetics to favor methylation in position 2 and 6 and to disfavor

position 3. This changed distribution alters the interaction of the glucose units within the polymer chain and also between polymer chains such that gelling can be obtained at body temperature (or lower) in a controlled fashion (see further details in section 5.2 Production process).

## 4.2 Analytical Information

### ***Is appropriate analytical information available on potentially toxic inherent constituents, external contaminants and nutrients?***

All Dow's grades of methyl cellulose, including those that gel as low as 31°C and as high as 65°C, are specified in the purity criteria for methyl cellulose (E 461) as a food additive (European Commission 2008). They are all derived from wood pulp. Table 1 below shows the purity criteria set for E 461 in the EU and how this compares with Dow's specification for methyl cellulose.

**Table 1 Comparison of Dow's Methyl Cellulose with EU Purity Criteria Set for E 461**

	<b>E 461 Methyl cellulose</b>	<b>Dow's methyl cellulose</b>
<b>Synonyms</b>	Cellulose methyl ether	Cellulose methyl ether
<b>Definitions</b>	Methyl cellulose is cellulose obtained directly from natural strains of fibrous plant material and partially etherified with methyl groups	Methyl cellulose is cellulose obtained directly from natural strains of fibrous plant material and partially etherified with methyl groups
<b>Chemical name</b>	Methyl ether of cellulose	Cellulose methyl ether CAS No. – 9004-67-5
<b>Chemical formula</b>	The polymers contain substituted anhydroglucose units with the following general formula: $C_6H_7O_2(OR_1)(OR_2)(OR_3)$ where $R_1, R_2, R_3$ each may be one of the following: — H — $CH_3$ — or $CH_2CH_3$	$[C_6H_7O_2(OH)_x(OCH_3)_y]_n$ where $x = 0.95$ to $1.55$ $y = 2.05$ to $1.45$ $x+y = 3.00$ ( $y =$ degree of substitution)
<b>Molecular weight</b>	From about 20,000 to 380,000 g/mol	Macromolecules: from about 20000 (n about 100) up to about 380,000 g/mol (n about 2,000)  Unsubstituted structural unit: 162.14  Structural unit with total degree of substitution of 1.45 : 182.44  Structural unit with total degree

		of substitution of 2.00 : 190.14
<b>Assay</b>	Content not less than 25 % and not more than 33 % of methoxyl groups (-OCH <sub>3</sub> ) and not more than 5 % of hydroxyethoxyl groups (-OCH <sub>2</sub> CH <sub>2</sub> OH)	Content not less than 25 % and not more than 33 % of methoxyl groups (-OCH <sub>3</sub> ) and not more than 5 % of hydroxyethoxyl groups (-OCH <sub>2</sub> CH <sub>2</sub> OH)
<b>Description</b>	Slightly hygroscopic white or slightly yellowish or greyish odourless and tasteless, granular or fibrous powder	Hygroscopic white or off-white, odourless fine granules, filaments or powder
<b>Identification</b>		
<b>A. Solubility</b>	Swelling in water, producing a clear to opalescent, viscous, colloidal solution. Insoluble in ethanol, ether and chloroform.  Soluble in glacial acetic acid	Swelling in water, producing a clear to opalescent, viscous, colloidal solution. Insoluble in ethanol, ether and chloroform.  Soluble in glacial acetic acid
<b>Purity</b>		
<b>Loss on drying</b>	Not more than 10 % (105 °C, 3 hours)	Not more than 10 % (105 °C, 3 hours)
<b>Sulphated ash</b>	Not more than 1.5 % determined at 800 ± 25 °C	Not more than 1.5 % determined at 800 ± 25 °C
<b>pH of a 1 % colloidal solution</b>	Not less than 5.0 and not more than 8.0	5.0-8.0 (see Table 2 below)
<b>Arsenic</b>	Not more than 3 mg/kg	Not more than 3 mg/kg (see Table 2 below)
<b>Lead</b>	Not more than 5 mg/kg	Not more than 2 mg/kg (see Table 2 below)
<b>Mercury</b>	Not more than 1 mg/kg	Not more than 1 mg/kg (see Table 2 below)
<b>Cadmium</b>	Not more than 1 mg/kg	Not more than 1 mg/kg (see Table 2 below)
<b>Heavy metals (as Pb)</b>	Not more than 20 mg/kg	Not more than 20 mg/kg (see Table 2 below)

***Is there an appropriate specification (including species, taxon etc. for living organisms) to ensure that the novel food marketed is the same as that evaluated?***

Yes. Table 2 below illustrates the specification of Dow's methyl cellulose.

**Table 2 Methyl Cellulose Specification and Analysis**

Test Item and Condition	Limit for Methyl Cellulose	Unit	Test Frequency	Method	Notes
Methoxyl	29.0-31.5	%		Current FCC	1
Methyl cellulose, active	93.5 Min	%		Calculated	2
Viscosity, 2% in water at 5 deg C	10-60,000	cPs		Brookfield / Ubbelohde (depending on the 2% viscosity)	
pH, 1% in Water	5.0-8.0			Current JECFA	
Moisture	5.0 Max	%		Current JECFA	
Residue on Ignition	1.5 Max	%		Current JECFA	
Residual Solvents	Pass		audit basis	Current USP	3
Sulfiting Agents, as Sulfur Dioxide	10 Max	ppm	audit basis	U.S. FDA 21 CFR	4
Lead	2 Max	ppm	audit basis	Current JECFA	
Arsenic	3 Max	ppm	audit basis	Current JECFA	
Mercury	1 Max	ppm	audit basis	Current JECFA	
Cadmium	1 Max	ppm	audit basis	Current JECFA	
Heavy Metals (as Pb)	20 Max	ppm	audit basis	Current USP/EP/JP	

**TEST REQUIREMENTS NOTES:**

1. DOWM 100755 = Current FCC Food Chemical Codex
2. Methyl cellulose, active content (soluble dietary fiber) = 100% -(% residue on ignition + % water).
3. Based on knowledge of the manufacturing process and controlled handling and storage, this product complies with ICH Q3C Residual Solvents Guidance requirements. The solvents listed as class 1, 2 and 3 by the US Pharmacopeia/National Formulary (USP/NF) are not used in the manufacturing process nor is there any potential for them to be present in this product.
4. Part 101, Appendix A of Monier-Williams procedure (with modifications) for sulfites in food, Center for Food and Safety and Applied Nutrition Food and Drug Administration (FDA), November, 1985.

***Is the information representative of the novel food when produced on a commercial scale?***

Yes. Table 3 provides details of the analysis of nine commercial lots of Dow's methyl cellulose and how these comply with the product specification. The viscosity of methyl cellulose varies significantly within the specification limits but in all cases meets the E 461 criteria set. This table also shows that product batch-to-batch data is consistent.

**Table 3 Analysis of Specific Lots of Methyl Cellulose Compared to the Product Specification**

Nominal Viscosity mPas		6000	6000	6000	400	4000	4000	40000	16000	50000	
Lot Number	Unit	XE22012NEB	XE23012NEA	XE24012NEA	YA071907F1	ZA171907F2	YC011907F2	XL041907F4	YG03012N11	YF07012NEA	Product Specification
Methoxyl	%	30.8	30.9	30.8	30.3	29.6	30.2	30.9	29.9	29.9	29.0 - 31.5
Methyl cellulose, active	%	97.9	97.7	97.4	97.8	98.4	98.2	98.1	97.6	97.5	93.5 min
Viscosity	cPs	7,565	6,200	5,965	445	4558	4,315	31,500	17,780	57,489	10 – 60,000
pH		6.1	6.4	6.4	7.4	6.6	7.2	7.8	6.5	7.2	5.0 - 8.0
Moisture	%	2	2.1	2.4	1.2	1.2	1.4	1.5	2.1	2.3	5.0 max
Residue on Ignition	%	0.2	0.3	0.3	1	0.4	0.4	0.4	0.3	0.2	1.5 max
Residual Solvents		Pass	Pass	Pass	audit basis	audit basis	audit basis	audit basis	audit basis	audit basis	Pass
Sulfiting Agents, as Sulfur Dioxide	ppm	< 10	< 10	< 10	audit basis	audit basis	audit basis	audit basis	audit basis	audit basis	< 10
Lead	ppm	< 2	< 2	< 2	< 1	< 1	audit basis	audit basis	< 2	audit basis	< 2
Arsenic	ppm	< 3	< 3	< 3	< 1	< 1	audit basis	audit basis	audit basis	< 3	< 3
Mercury	ppm	<1	<1	<1	< 0.1	< 0.1	audit basis	audit basis	audit basis	<1	<1
Cadmium	ppm	<1	<1	<1	< 0.1	< 0.1	audit basis	audit basis	audit basis	<1	<1
Heavy Metals (as Pb)	ppm	<20	<20	<20	< 10	< 10	audit basis	audit basis	audit basis	audit basis	<20

## 5 Effect of the Production Process Applied to the Novel Food

### *Does the novel food undergo a production process?*

Yes. All Dow's methyl cellulose grades, including food additive (E 461) grades, are a result of a production process which is described in detail below.

Dow's methyl cellulose production process is a continuous batch-to-batch process. The initial batch includes the initial grinding of wood pulp through the reactor unit operation. The reactor slurry is introduced into the continuous portion of the process which includes filtration through the milling unit operations. The final batch process includes blending and packaging. There is traceability forward from the raw materials through to the final batch and backward from final batches through to the raw materials.

Master production records are in place for each product family and detailed batch records are created for each final batch. In-process and final product sampling and testing plans are in place to ensure appropriate monitoring of

defined critical process and product parameters that occur within each unit operation of the production process. Validated cleaning procedures are in place for use after maintenance activities, shutdown activities, and after product campaign changes.

Quality critical equipment is defined within the facility as those necessary to manufacture, test or ensure compliance with product specifications. Malfunction or improper operating of equipment may result in an altered or suspect product that may be unacceptable for sale as intended use. A quality critical instrument is further defined as a system, including measuring device and hardware/software response, used to control the specific measured parameter.

All quality critical equipment and instrumentation are on a documented schedule for calibration and maintenance. The schedule is established by considering such things as manufacturer's recommendation, past experience, nature of the process, or other pertinent factors. Non-routine maintenance activities are also scheduled when specific problems such as leaks, known or suspected equipment failure, or visual inspections show a need.

***Is there a history of use of the production process for the food?" If not, does the process result in a significant change in the composition or structure of the novel food compared to its traditional counterpart?***

Yes. This production process has been used for a long time (since the mid-1950's) for the production of methyl cellulose as a food additive (E 461).

***Is information available to enable identification of the possible toxicological, nutritional and microbiological hazards arising from use of the process? Are there means identified for controlling the process to ensure that the novel food complies with its specification?***

The production facility has an on-going Hazard Analysis Critical Control Point (HACCP) programme in place to ensure the safety of products used in food applications. As part of this programme, potential hazards associated with raw materials, processing, storing and distribution of the product to customers have been identified and critical control points established to control these hazards. These control points ensure that the production and distribution of safe products is routinely monitored to minimise any significant risks. See further details below.

## 5.1 Raw Materials

The important raw materials for the manufacture of methyl cellulose are as follows: purified cellulose (derived e.g. from wood pulps), methyl chloride, caustic soda solution, hydrogen chloride, sodium bicarbonate and water.

Methyl chloride is a colourless, odourless gas at atmospheric conditions, but is stored as a liquid under pressure. Methyl chloride is flammable. The material is transferred to the cellulose reactors when required, and the transfer is monitored with instruments to assure proper operation.

Pulp is received and ground in the pulp grinders. The pulp is then transferred as needed to the reactors.

Caustic soda solution is used to create alkali cellulose. The caustic is transferred to the cellulose reactors when it is needed and the transfer is monitored with instrumentation to assure proper operation.

Hydrogen chloride is used in the production of low viscosity products in the low viscosity reaction. Residual hydrogen chloride is neutralised with sodium bicarbonate.

Water is used as a solvent in the purification process to remove impurities.

## 5.2 Production Process

### Reaction

Pulp is added to the reactor followed by caustic soda solution to produce alkali cellulose. The appropriate amount of methyl chloride is then added to produce methyl cellulose. The amount of each raw material is dictated by product specific recipes. The mass is agitated and a specific time/temperature profile is followed until the proper methyl cellulose is produced. The mass is slurried in water and transferred to a slurry hold tank. The reaction cycle is then ready to start over again.

### Washing

The slurried material is transferred to a series of filters. The filters use hot water to wash the sodium chloride and residual organics from the methyl cellulose material. To ensure proper removal of salt and organics from the methyl cellulose, process variables are monitored. The filters are enclosed to maintain a temperature high enough to prevent the methyl cellulose from gelling.

### Drying

The methyl cellulose wet cake from the filter step is broken up and discharged into a dryer. The feed rate and dryer temperature are set and monitored by computer control to ensure a dry product.

### **Size Reduction**

The dry material is then ground to achieve the desired particle size.

### **In-Process Storage**

Due to the wide variety of methyl cellulose products produced, there are many storage silos that are used to store the methyl cellulose prior to packaging. The number of storage vessels allows for isolation of products.

### **Batch Isolation and Homogenisation**

As a result of the product variation imposed by the use of a natural raw plant material, e.g. wood pulp, and the continuous batch-to-batch nature of this process, it is necessary to isolate an appropriate quantity of product, make any required adjustments to finished properties and mix to assure homogeneity. The homogenisation step is performed in blenders following the in-process silo storage.

### **Methyl Cellulose Lower Viscosity (LV) Products**

If methyl cellulose products are to be generated with a 2% viscosity smaller than 500mPas, the products are intentionally subjected to hydrochloric acid in order to lower the final viscosity of the product. The reaction is monitored to obtain the desired viscosity. Sodium bicarbonate is used as a buffering agent to neutralise the hydrogen chloride at the end of the reaction.

***Has the process the potential to alter the levels in the novel food of substances with an adverse effect on public health?***

Yes. HACCP is applied, as discussed above.

***After processing is the novel food likely to contain micro-organisms of adverse public health significance?***

No. See microbiological information in section 10.



## **6 History of the Organism Used as the Source of the Novel Food**

***Is the novel food obtained from a biological source, i.e. a plant, animal or micro-organism?***

Yes, Dow's methyl cellulose is derived from highly purified cellulose from plants (e.g. softwood trees). This plant source is not genetically modified and has a history of use in the EU to produce food additive E 461.

***Has the organism used as the source of the novel food been derived using genetically modified material?***

No.

***Is the source organism characterised?***

The cellulose from plants is a high purity, specialty cellulose designed for producing food and pharmaceutical products for human consumption. The cellulose is derived from plant material (e.g. softwood trees). Dow manufactures methyl cellulose globally and sources purified cellulose globally. The suppliers have land and forest management programmes in place to ensure protection of waterways near land being managed and preservation of natural wild life. This is a GMO-free product and cannot be manufactured with pulps containing cotton. Cellulose pulp from plants is already used as a source of cellulose in methyl cellulose which is then used as food additive E 461 in the EU.

***Is there information to show that the source organism and/or foods obtained from it are not detrimental to human health?***

Yes. Highly purified cellulose from plants has been used as a source of methyl cellulose as a food additive E 461 in the EU for many years without any safety concerns.

## 7 Anticipated Intake/Extent of Use of the Novel Food

### 7.1 Proposed Use of Methyl Cellulose

The proposed application of methyl cellulose as a novel food ingredient is primarily in cold, wet, medium viscosity type foods such as ice-cream, flavoured milk drinks, cold desserts, smoothie-type beverages, yogurts, yogurt drinks and cold wet soups. Predicted intakes of methyl cellulose as a novel food ingredient were estimated from the proposed food groups shown in Table 4. Anticipated use levels in each of these food categories ranges from 1.5% to 2%.

**Table 4 Proposed Use of Methyl Cellulose as a Novel Food Ingredient**

Food Category	Anticipated Use level (%)
Ice-cream	1.5 – 2
Milk beverages (e.g. flavoured milk drinks, milkshakes)	
Puddings (e.g. cold desserts, rice pudding, custard, sponge cake)	
Smoothie type beverages (e.g. fruit smoothies)	
Yogurt	
Yogurt beverages (e.g. drinking yogurts)	
Wet soups (cold)	

### 7.2 Estimation of Predicted Intake of Methyl Cellulose from Proposed Food Uses

Four cross-sectional food consumption surveys in the United Kingdom and the Republic of Ireland were used to estimate intake exposure to methyl cellulose:

- National Teens' Food Survey (Republic of Ireland)
- National Children's Food Survey (Republic of Ireland)
- North South Ireland Food Consumption Survey (Adult survey: Republic of Ireland and Northern Ireland)
- National Diet and Nutrition Survey: Children Ages 1.4 to 4.5 years (British (NDNS) Toddlers' survey)

The three Irish Surveys were carried out by the Irish Universities Nutrition Alliance (IUNA), a formal alliance of the academic nutrition centres at University College Cork (UCC), University College Dublin (UCD)/Trinity College Dublin (TCD) and the University of Ulster (UU). As there is currently no Irish food consumption survey covering young children (i.e. less than five

years), the National Diet and Nutrition Survey of British Children was used for this population sample. The British food consumption survey was carried out by the by the Social Survey Division of the Office of Population Censuses and Surveys and the Micronutrient Status Group of the Medical Research Council for the UK government.

Details of each survey are shown in Table 5 below. Taken together, these four databases provide habitual food and drink consumption of 4515 subjects with an age range of 1.5 – 64 years in the United Kingdom and the Republic of Ireland.

**Table 5 Overview of Food Consumption Surveys used to Estimate Predicted Intake of Methyl Cellulose**

Food Consumption Survey	Year of data collection	Sample size (n)	Age (yrs)	Data collection	Sampling	Participant response rate	Reference
National Teens' Food Survey  (Republic of Ireland)	2005- 2006	441 M: 224 F: 217	13-17	7-day semi-weighed food diary	Participants selected from 32 secondary schools <sup>1</sup>	63%	Methodology & summary report available at: <a href="http://www.iuna.net">www.iuna.net</a>
National Children's Food Survey  (Republic of Ireland)	2003-2004	594 M: 293 F: 301	5-12	7-day weight food diary	Participants selected from 28 primary schools <sup>1</sup>	66%	Methodology & summary report available at: <a href="http://www.iuna.net">www.iuna.net</a>
North South Ireland Food Consumption Survey  (Republic of Ireland & Northern Ireland)	1997-1999	1379 M: 662 F: 717 (Excl. pregnant women)	18-64	7-day estimated food record	Random sampling using the electoral register	63%	Harrington et al., 2001  Methodology & summary report available at: <a href="http://www.iuna.net">www.iuna.net</a>
National Diet & Nutrition Survey: Children Ages 1.5 to 4.5 Years  (Great Britain)	1992-1993	1675 M:848 F:827	1.5-4.5	4-day weighed records collected over 12 months  (recorded by parents)	Nationally representative sample  Multi-stage random probability design, with postal sectors as first stage units.	81%	Gregory et al., 1995

<sup>1</sup>Schools were selected from a database of secondary schools available from the Department of Education and Science. Analysis of the demographic characteristics of the Irish teenage and children survey samples, which were selected from schools, were shown to a representative sample of the Irish teenagers and Irish children with respect to age, sex, social class, socioeconomic group and geographical compared to national census data.

Predicted average daily intakes of methyl cellulose using the above food groups (Table 4) were estimated using Creme Food<sup>®</sup> software<sup>1</sup>, a web-based validated software program purpose built to carry out food chemical exposure assessments using a deterministic (point estimate) as well as a probabilistic (stochastic) approach (McNamara et al 2003). Raw data in its most disaggregated form (at the level of each eating event) from all of the above food consumption surveys are contained within the software program.

Food groups used in the exposure assessment were created using food codes, or food group codes where applicable, from each food consumption survey database. Food codes of homemade foods (e.g. homemade soup) were excluded. A list of all food codes and corresponding food groups used in the exposure assessment of methyl cellulose is included in Appendix E.

In the case of cold, wet soups, for which there were no food codes in the above food consumption databases, intake data from hot, wet soup consumption was used as a proxy measure of cold, wet soup consumption. It is noteworthy that hot wet soup is not a suitable food vehicle (technologically) for methyl cellulose.

Smoothie-type beverages were not included in the intake assessment using the Irish adult or British Toddler survey as there were no food codes for smoothies in either survey. This reflects a likely absence or lack of consumption of these products during the survey periods. In the case of toddlers, smoothies are unlikely to constitute a significant source of consumption. This is corroborated by a search of Mintel's Global New Produce Database (GNPD) which yielded 139 new smoothie product launches in Europe from October 2010 – October 2011, none of which were positioned to toddlers<sup>2</sup>. In the absence of smoothie consumption data from the Irish adult survey, as well as an absence of published data on smoothie consumption, it is plausible to assume that smoothie consumption from the Irish teens' survey is a reasonable approximation of adult smoothie consumption.

When estimating exposure to a (novel) food ingredient, Creme Food<sup>®</sup> considers all eating events in order to determine the daily average intake of a food ingredient, via defined food groups, for every subject in each survey. Average daily intakes are calculated per subject by combining the amount of a food consumed at each single eating occasion with the corresponding concentration of methyl cellulose. Statistics are then calculated for exposure

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<sup>1</sup> [www.cremesoftware.com](http://www.cremesoftware.com)

<sup>2</sup> [www.gnpd.com](http://www.gnpd.com). Search term: 'smoothies; category: juice; search period: October 2010-October 2011.

for the entire population (All-Person Consumption) as well as consumers only (All-Users Consumption)<sup>3</sup>.

Seven exposure assessments were carried out for each concentration scenario of methyl cellulose using all food groups. Six (deterministic) assessments used fixed concentration scenarios of methyl cellulose in all food groups: 1.5%, 1.6%, 1.7%, 1.8%, 1.9% and 2.0%. One (probabilistic) assessment used a randomly assigned concentration of methyl cellulose from a uniform concentration distribution between 1.5 and 2.0% at each eating event, which could be different for the same food at each eating event. In all cases (deterministic / probabilistic), a 100% probability of presence of methyl cellulose in each food group was assumed.

Predicted intake data (i.e. average daily intakes) were calculated for the total population, consumers only as well as for males and females. In addition, the contribution of each food group to the overall predicted mean intakes of methyl cellulose as a novel food ingredient was assessed.

## **Results**

Predicted intakes of methyl cellulose (average daily intakes ( $\pm$ SE)) are presented as absolute intakes (mg/day) in Appendix A as well as intakes expressed per kilogram body weight per day in Appendix B.

Intakes are expressed as mean as well as high level consumption (i.e. 90th, 95th and 97.5th percentiles) for the total population (All-Person Consumption) as well as consumer only intakes (All-Users Consumption).

Predicted average daily intakes of methyl cellulose for each survey, based on fixed concentration scenarios of 1.5, 1.6, 1.7, 1.8, 1.9 and 2.0% (deterministic approach) are presented in Tables A-1 to A-6 respectively (Appendix A), expressed as mg/d, and in Tables B-1 to B-6 respectively (Appendix B), expressed as mg/kg bw/day.

Predicted average daily intakes of methyl cellulose for each survey, based on a randomly assigned concentration from a uniform distribution between 1.5 and 2% at each eating event (probabilistic approach) are presented in Table A-7 (Appendix A), expressed as mg/d, and in Table B-7 (Appendix B), expressed as mg/kg bw/day.

A breakdown of predicted average daily intakes for males and females, based on fixed concentration scenarios of 1.5, 1.6, 1.7, 1.8, 1.9 & 2.0% (deterministic approach), is presented in Tables A-8 to A-13 and Tables A-15 to A-20

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<sup>3</sup> All person (total population) consumption estimates refers to estimated intakes for all survey participants regardless of whether they consumed a food assumed to contain methyl cellulose. All-Users (consumers only) consumption refers to estimated intakes for participants who consumed one or more of the foods assumed to contain methyl cellulose.

(expressed as mg/day for males and females, respectively), and Tables B-8 to B-13 and B-15 to B-20 (expressed as mg/kg bw/day for males and females, respectively).

A breakdown of predicted average daily intakes for males and females, based on a randomly assigned concentration from a uniform distribution between 1.5 and 2% (probabilistic approach), is presented in Table A-14 and Table A-21, (expressed as mg/day for males and females, respectively ) and Table B-14 and B-21 (expressed as mg/kg bw/day for males and females, respectively).

The contribution of each food group to overall mean predicted intakes of methyl cellulose is presented in Tables A-22 to A-25 (expressed as mg/day) and Tables B-22 to B-25 (expressed as mg/kg bw/day) for each food survey. These data were derived by randomly assigning a concentration of methyl cellulose from a uniform concentration distribution between 1.5% and 2% (probabilistic approach).

### ***Deterministic Intake Estimates***

The highest intake (97.5th percentile; consumers only) of methyl cellulose is observed when the highest concentration (2%) is assumed (Tables A-6 & B-6).

The highest predicted intake (97.5th percentile; consumers only), expressed as absolute intakes, is  $4479 \pm 436$  mg/day among Irish teenagers (Table A-6).

When intakes are expressed on a body weight basis, the highest predicted intake (97.5th percentile; consumers only), is observed among British toddlers  $293 \pm 14.9$  mg/kg bw/day (Table B-6).

When split by gender, Irish *male* teenagers ( $4973 \pm 396$  mg/day) (Table A-13) and British *female* toddlers ( $4474.53 \pm 492.67$  mg/day) (Table A-20) had the highest intakes (97.5<sup>th</sup> percentile; consumers only). When expressed on a body weight basis, British *male* toddlers ( $275 \pm 12.92$  mg/kg bw/day) (Table B-13) and British *female* toddlers ( $326 \pm 28.87$  mg/kg bw/day) (Table B-20) had the highest intakes.

### ***Probabilistic Intake Estimates***

Highest intake estimates using a probabilistic approach (97.5<sup>th</sup> percentile; consumers only using a randomly assigned concentration of methyl cellulose from a uniform concentration distribution between 1.5 and 2%) are observed among Irish *male teenagers* ( $4273.3 \pm 322.5$  mg/day; Table A-14) when expressed as absolute intakes. When expressed per kilogram body weight, highest intakes are observed among British *female toddlers* ( $282.54 \pm 25.77$  mg/kg bw/day; Table B-21).

Milk beverages contributed the highest mean intake of methyl cellulose among Irish adults (Table A-22, B-22), Irish children (A-23, B-23) and Irish teenagers (Table A-24, B-24) whereas yogurt beverages contributed the highest mean intake among British toddlers (Table A-25, B-25).

### **7.3 Estimation of Baseline Intakes of Methyl Cellulose as a Food Additive**

Methyl cellulose is permitted for use as a food additive in the EU (E461) as per Annex 1 (generally permitted food additives) of the miscellaneous food additives Directive 95/2/EC in accordance with good manufacturing practice (European Commission 1995). Thus, it is generally permitted in foodstuffs except those where no food additives are permitted. A group Acceptable Daily Intake (ADI) 'not specified' was assigned by the former Scientific Committee on Food on five modified celluloses, including methyl cellulose in 1992 (SCF 1994) which was largely based on evaluation by JECFA (The Joint FAO/WHO Expert Committee on Food Additives). There are no published intake exposure data on its use as a food additive.

Crude baseline intakes of methyl cellulose as a food additive were estimated using the food groups in Table 6. These food groups were included in the assessment on the basis of the applicant's expert judgement on foods likely to contain methyl cellulose as a food additive as well as taking regulatory considerations into account with regard to usage restrictions.

In the absence of maximum permitted levels of methyl cellulose laid down in the additives legislation, as well as a lack of data on actual usage levels of methyl cellulose as a food additive, plausible technological levels of use based on the applicant's expert judgement were assumed. These ranged from 0.1 to 0.5% in each food group (Table 6).

An assessment of baseline intakes (average daily intakes) of methyl cellulose as a food additive was carried out using Creme Food<sup>®</sup> software and the food consumption survey databases described previously (Table 5). Both deterministic (point estimate) and probabilistic (stochastic) intake estimates were calculated using the approach described in section 7.2 above.

The food groups in Table 6 were created from food codes, or food group codes where applicable, in each food consumption survey. Food codes of homemade foods were excluded. A list of all food codes and corresponding food groups used in the exposure assessment is included in Appendix F.

**Table 6 Food Groups Used in Intake Assessment of Methyl Cellulose as a Food Additive**

Food Group	Estimated Use Level (%)
<b>Bakery Products:</b> Include breads* & rolls, doughnuts, cookies and tortillas. <i>*All breads prepared solely with wheat flour, water, yeast or leavens, and salt, if applicable, were excluded.</i>	0.1 – 0.5%
<b>Extruded Food Applications:</b> Include onion rings, seafood products*, potato products and patties (pastries that contain various fillings e.g. sausage rolls, vegetable pastries etc.). <i>*Seafood products exclude all unprocessed fish, crustaceans and molluscs including those that are frozen and deep frozen.</i>	
<b>Instant Desserts:</b> Include instant cheesecake and instant puddings.	
<b>Salad dressings &amp; Marinades:</b> Include dry mix salad dressings, pourable salad dressings and marinades.	
<b>Soups, Sauces &amp; Gravies:</b> Include cheese sauces, cream sauces, dry mix gravies, prepared gravies, red (tomato) sauces and soups.	

Six exposure assessments were carried out for each concentration scenario of methyl cellulose as a food additive. Five (deterministic) assessments used fixed concentration scenarios: 0.1%, 0.2%, 0.3%, 0.4% and 0.5%. One (probabilistic) assessment used a randomly assigned concentration of methyl cellulose from a uniform concentration distribution between 0.1 and 0.5%. In all cases (deterministic / probabilistic approach), a 100% probability of presence of methyl cellulose in each food group was assumed.

Baseline intakes of methyl cellulose as a food additive (average daily intakes ( $\pm$ SE)) were calculated for the total population, consumers only as well as for males and females. In addition, the contribution of each food group to overall estimated intakes was assessed.

### **Results**

Baseline additive intakes are presented in Appendix C (expressed as mg/day) as well as Appendix D (expressed as mg/kg body weight per day). Intakes are expressed as mean as well as high level consumption (i.e. 90th, 95th and 97.5th percentiles) for the total population (All-Person Consumption) as well as consumer only intakes (All-Users Consumption).

Intakes based on fixed concentration scenarios of 0.1, 0.2, 0.3, 0.4 and 0.5% (deterministic approach) are presented in Tables C-1 to C-5 (Appendix C), expressed as mg/day, and Tables D-1 to D-5 (Appendix D), expressed as mg/kg bw/day for each food survey.



Intakes based on a randomly assigned concentration from a uniform distribution from 0.1 to 0.5% at each eating event (probabilistic approach) are presented in Table C-6 (Appendix C), expressed as mg/day, and Table D-6 (Appendix D), expressed as mg/kg bw/day, for each food survey.

A breakdown of average daily intakes for males and females based on fixed concentration scenarios of 0.1, 0.2, 0.3, 0.4 and 0.5% (deterministic approach) is presented in Tables C-7 to C-11 and C-13 to C-17 (expressed as mg/day for males and females, respectively), and Tables D-7 to D-11 and Tables D-13 to D-17 (expressed as mg/kg bw/day for males and females, respectively).

A breakdown of average daily intakes for males and females, based on a randomly assigned concentration from a uniform distribution between 0.1 and 0.5% (probabilistic approach), is presented in Table C-12 and C-18, (expressed as mg/day for males and females, respectively), and Table D-12 and D-18 (expressed as mg/kg bw/day for males and females, respectively).

The contribution of each food group to estimated baseline intakes of methyl cellulose as a food additive is presented in Tables C-19 to C-22 (expressed as mg/day) and D-19 to D-22 (expressed as mg/kg bw/day) for each food survey. These data were derived by randomly assigning a concentration of methyl cellulose from a uniform concentration distribution between 0.1% and 0.5% (probabilistic approach).

### ***Deterministic Intake Estimates***

The highest estimated baseline intake of methyl cellulose as a food additive is observed when the highest concentration (0.5%) is assumed (Tables C-5 & D-5).

The highest intake (97.5th percentile; consumers only), expressed as absolute intakes, is  $2141.95 \pm 54.83$  mg/day among Irish adults (Table C-5).

When intakes are expressed on a body weight basis, the highest intake (97.5th percentile; consumers only), is observed among British toddlers  $67.62 \pm 1.95$  mg/kg bw/day (Table D-5).

When split by gender, Irish *male* adults ( $2334 \pm 71$  mg/day) (Table C-11) and Irish *female* adults ( $1615 \pm 116$  mg/day) (Table C-17) had the highest intakes (97.5th percentile; consumers only). When expressed on a body weight basis, British *male* toddlers ( $66.50 \pm 2.64$  mg/kg bw/day) (Table D-11) and British *female* toddlers ( $69.63 \pm 2.27$  mg/kg bw/day) (Table D-17) had the highest intakes.

### ***Probabilistic Intake Estimates***

Highest intake estimates using a probabilistic approach (97.5<sup>th</sup> percentile; consumers only using a random concentration of methyl cellulose from a uniform concentration distribution between 0.1 and 0.5%) are observed among Irish *male adults* (1379.2± 44.5 mg/day; Table C-12) when expressed as absolute intakes. When expressed as intakes per kilogram body weight, highest intakes are observed among British *female toddlers* (41.89±1.58 mg/kg bw/day; Table D-18).

Bakery products contributed to the highest mean intake of methyl cellulose as a food additive among Irish adults (Table C-19, D-19), Irish children (Table C-20, D-20) Irish teenagers (C-21, D-21) and British toddlers (Table C-22, D-22).

### ***Conclusion***

The highest overall predicted intake of methyl cellulose (97.5<sup>th</sup> percentile; consumers only at a fixed concentration of 2%) using a deterministic approach is observed for Irish *male teenagers* (4973±396 mg/day) when expressed as absolute intakes. When expressed as intakes per kilogram body weight, highest intakes (326±28.87 mg/kg bw/day) are observed among British *female toddlers*.

The highest estimated baseline intake of methyl cellulose as a food additive (97.5<sup>th</sup> percentile; consumers only at a fixed concentration of 0.5%) using a deterministic approach is observed among Irish *adult males* (2334±71 mg/day) when expressed as absolute intakes. When expressed as intakes per kilogram body weight, highest intakes are observed among British *female toddlers* (69.63±2.27 mg/kg bw/day).

Deterministic intake estimates from both assessments are considered to be very conservative and worst case estimates. The food groups used in both exposure assessments (Appendix E & F) encompass a broad range of food codes. Both assessments assumed that methyl cellulose is *a/ways* present at a maximum fixed concentration in all foods, and that *all* foods are consumed in high amounts. This is very unlikely to be the case in practice. In addition, use of hot, wet soup consumption as a proxy for cold wet soup consumption is likely to overestimate cold, wet soup consumption.

Using a probabilistic approach, highest predicted intakes as a novel ingredient (4273.3±322.5 mg/day; 282.54±25.77 mg/kg bw/day) and highest baseline intakes as a food additive (1379.2±44.5 mg/day; 41.89±1.58 mg/kg bw/day) whereby variability in the concentration of methyl cellulose is taken into account, are considered to be more plausible whilst still maintaining a degree of conservatism (i.e. assuming 100% probability of presence of methyl cellulose in all foods).

## **8 Information from Previous Human Exposure to the Novel Food or Its Source**

***Is there information from previous direct, indirect, intended or unintended human exposure to the novel food or its source which is relevant to the EU situation with respect to production, preparation, population, lifestyles and intakes?***

Yes. As a food additive (E 461) methyl cellulose has been used since mid 1950's.

A qualitative survey of food additive usage patterns in a generally representative sample of 5684 processed foods on the Irish food market recorded in the Irish National Food Ingredient Database showed that less than 0.1% of foods contained methyl cellulose (FSAI, 2001). There are no published intake data on methyl cellulose.

***Is there information to demonstrate that exposure to the novel food is unlikely to give rise to mitochondrial, toxicological and/or allergenicity problems?***

Yes, adequate information is available to show that negative effects regarding microbiology, toxicology and allergy are not expected. See toxicology section 11.

## **9 Nutritional Information on the Novel Food**

As a food ingredient, methyl cellulose fits under the 2<sup>nd</sup> category of material constituting dietary fibre as per the definition laid down in Annex II of Directive 90/496/EEC on nutrition labelling (European Commission 1990) (as amended) as detailed below:

'Fibre' means carbohydrate polymers with three or more monomeric units, which are neither digested nor absorbed in the human small intestine and belong to the following categories:

- edible carbohydrate polymers naturally occurring in the food as consumed;
- edible carbohydrate polymers which have been obtained from food raw material by physical, enzymatic or chemical means and which have a beneficial physiological effect demonstrated by generally accepted scientific evidence;
- edible synthetic carbohydrate polymers which have a beneficial physiological effect demonstrated by generally accepted scientific evidence.

***Is there information to show that the novel food ingredient is nutritionally equivalent to existing foods that it might replace in the diet?***

Methyl cellulose is a dietary fibre and will be added to foodstuffs for its nutritional properties and to increase satiety (see further details in last paragraph below). It is not intended to replace any existing food ingredient in the diet.

***Is there information to show that the novel food does not affect the bioavailability of nutrients from diet or have any adverse physiological effects? If no, is information available to allow a balance to be made between risks and benefits?***

No studies were located that directly address the effect of methyl cellulose on nutrient bioavailability, however, the following comments can be made. A review of studies show that several extended studies in various species, while not directly assessing vitamin and mineral uptake, show no effects from methyl cellulose on their long-term health and condition. A study with five male volunteers given 250 mg/kg bw of methyl cellulose for 23 days indicated that all of the biochemical parameters tested such as urea, electrolytes, bilirubin, aspartate transaminase alkaline phosphatase protein, albumin, calcium, uric acid, phosphate, creatinine remain unchanged (Eastwood et al. 1990). The ability of methyl cellulose to interfere with vitamin uptake in the gut was investigated in rats that were either normal or depleted of either Vitamin A or thiamine. These vitamins were chosen to represent both water and oil soluble vitamins. The four groups of 10 rats (5 male and 5 female) were given 50 mg of methyl cellulose for 28 days. Interference of methyl cellulose with vitamin absorption was determined by measuring growth response. Results indicated that methyl cellulose does not interfere with vitamin uptake (Ellingson and Massengale, 1952).

***Is there information to allow assessment to be made of the nutritional impact of the introduction of the novel food?***

Dow's methyl cellulose has been tested for its effect on initiating a satiety response in a blinded study of fasted healthy volunteers (32 subjects; Conference presentation, Roberta Re, Vitafoods, May 10-12, 2011, Geneva, Switzerland). Two hours after ingestion, subjects showed an average of a 13% reduction in caloric intake compared with an equal volume of water or of a non-gelling methyl cellulose of matching viscosity. To date, there are no published studies on Dow's methyl cellulose which measured compensatory consumption at later meals or for the effect of its administration over several days.

## 10 Microbiological Information on the Novel Food

### ***Is the presence of any microorganisms or their metabolites due to the novelty of the product/process?***

Not applicable. Dow's methyl cellulose is produced without the aid of microbiological processes (i.e. fermentation). Therefore, no microorganisms or their metabolites are anticipated. The production process of methyl cellulose is strictly monitored and controlled and a hygienic procedure is followed according to Hazard Analysis Critical Control Point (HACCP). The production facility has an on-going HACCP programme in place to ensure the safety of products used in food applications. As part of this programme, potential hazards associated with raw materials, processing, storing and distribution of the product to customers have been identified and critical control points to control these hazards and ensure the production and distribution of safe products are routinely monitored to minimise the significant risks. Therefore contamination with microorganisms is not expected.

### ***Is there information to show that the novel food is unlikely to contain microorganisms and/or their metabolites of adverse public health significance?***

Yes. See product microbiological specification and testing results below in Tables 7 and 8.

**Table 7 Dow's Methyl Cellulose Microbiological Specification**

Test Item and Condition	Limit	Unit	Test Frequency	Method	Notes
Total Aerobic Microbial Count	500 Max	cnt/g	audit basis	Current USP	
Total Combined Mold & Yeast	500 Max	cnt/g	audit basis	Current USP	
Staphylococcus Aureus, negative	Pass		audit basis	Current USP	
Pseudomonas Aeruginosa, negative	Pass		audit basis	Current USP	
Salmonella Species, negative	Pass		audit basis	Current USP	
Escherichia Coli, negative	Pass		audit basis	Current USP	
Total Coliforms	10 Max	cnt/g	audit basis	Current USP	
Listeria Monocytogens	100 Max	cnt/g	audit basis	BAM	6
Clostridium Botulinum	100 Max	cnt/g	audit basis	BAM	7
Bacillus Cereus	100 Max	cnt/g	audit basis	BAM	8

#### **TEST REQUIREMENTS NOTES:**

6. BAM – US FDA Bacteriological Analytical Manual, 8th Ed, Revisions A, 1998

7. BAM – US FDA Bacteriological Analytical Manual, 8th Ed, Revisions A, 1998

8. BAM – US FDA Bacteriological Analytical Manual, 8th Ed, Revisions A, 1998

BAM = Bacteriological Analytical Manual

**Table 8 Analysis of Specific Lots of Methyl Cellulose Compared to the Product Specification**

<b>Blender Number</b>	<b>5920</b>	<b>5921</b>	<b>5922</b>	<b>5923</b>	<b>Product Specification</b>
<b>Lot Number</b>	<b>XE22012NEA</b>	<b>XE22012NEB</b>	<b>XE23012NEA</b>	<b>XE24012NEA</b>	
Aerobic Count CFU/g	<50	<50	<50	<50	500 max
Yeast-Mold Count CFU/g	<50	<50	<50	<50	500 max
Salmonella	absent	absent	absent	absent	absent
E. Coli	absent	absent	absent	absent	absent
S. aureus	absent	absent	absent	absent	absent
P. aeruginosa	absent	absent	absent	absent	absent

***Is the novel food likely to be confused with existing foods? If no, is information available to allow the development of procedures to ensure that the novel food is appropriately handled, cooked or processed before consumption?***

Not applicable.

***Are the procedures for handling, cooking or processing the existing food adequate to ensure safety if applied to the novel food?***

Yes. See information on processing in section five.

## 11 Toxicological Information on the Novel Food

### ***Is there information from a range of toxicological studies appropriate to the novel food to show that the novel food is safe under anticipated conditions of preparation and use?***

Yes. Although no toxicity studies are known to demonstrate the equivalence in safety between different positional distributions of methyl groups on the glycosyl monomer units (See Section 4.1), it may be concluded that, considering the length of the methyl cellulose molecule, the knowledge that the methyl cellulose molecule will not be altered in the gastrointestinal tract, and a lack of systemic availability of methyl cellulose upon ingestion, no difference in safety exists. Dow's methyl cellulose meets the EU purity criteria for methyl cellulose E 461 (European Commission 2008) and all grades are expected to have the same safety profile. Toxicological information on methyl cellulose is provided below.

Dow's methyl cellulose used as a food ingredient is expected to significantly increase the amount of consumption beyond its current use as a food additive. Based on the information obtained from animal and human studies in combination with the history of use of methyl cellulose as food additive and other evaluations, the intake of the amounts of methyl cellulose in the proposed enriched food products with the proposed substitution ranges is considered to be safe. Furthermore, it is expected that the consumption of methyl cellulose as a source of fibre will be self-limiting.

Safety considerations, such as choking risk, overdose hazard, and gastrointestinal intolerance are addressed in section 11.2. It was concluded that methyl cellulose does not pose a significant choking or overdose hazard. The effect on the human gut regarding gastrointestinal intolerance and laxation with increased consumption of Dow's methyl cellulose is expected to be similar to any individual consuming a high fibre diet.

### ***Is there information which suggests that the novel food might pose an allergenic risk to humans?***

No, no allergic risk is expected (see further information in section 11.1.5 Allergenicity).

### ***Is there sufficient information to allow the potential allergenicity of the novel food to be monitored?***

Not applicable.

***Has the level of allergenicity been determined in a controlled trial?***

No, not applicable.

**11.1 Review of Toxicological Data Available for Methyl Cellulose**

The information provided below includes findings of published safety evaluations of methyl cellulose by authoritative bodies as well as a comprehensive review of toxicological data available for methyl cellulose and several analogues.

**11.1.1 Safety Evaluation**

Comprehensive reviews on the safety of methyl cellulose, which includes reviews of available toxicology literature on methyl cellulose and its analogues, have been conducted by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the Cosmetic Ingredient Review Board (CIR), as described below.

Methyl cellulose was reviewed as a food additive by JECFA. Its findings were published as: WHO Food Additives Series: 26 "Toxicological Evaluation of Certain Food Additives and Contaminants" prepared by the 35th meeting (JECFA, 1990). . A group ADI of "not specified" for modified celluloses was established at this meeting Ethyl cellulose, ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose, methyl ethyl cellulose, sodium carboxymethyl cellulose, and cross-linked sodium carboxymethyl cellulose were added at the fifty-ninth meeting in 2002 (JECFA 2003). The toxicological monograph for the JECFA evaluation concluded that modified celluloses as a group are of very low toxicity. Thus, the JECFA review and evaluation supports a general interpretation of the toxicological properties of modified celluloses as reflecting the non-absorption of the ingredients and hence, their general non-bioavailability. Dow believes that the literature on various substitutions and viscosities of methyl cellulose and other modified celluloses, as discussed below, supports this interpretation of the data based on similar pharmacokinetic and toxicological profiles.

JECFA does note "The ability to produce laxation should be taken into account when using these substances as food additives." The JECFA report notes "At higher doses diarrhoea has been reported in some subjects but in others constipation developed. Studies in humans did not exceed the addition of 30 g/person/day. An intake of 30 g/day has been recommended as the upper safe level of dietary fibre in general."

This term "ADI not specified" is applicable to a food substance of very low toxicity which, on the basis of the available data (chemical, biochemical, toxicological and other), the total dietary intake of the substance arising from



its use at the levels necessary to achieve the desired effect and from its acceptable background in food does not, in the opinion of JECFA, represent a hazard to health. For that reason, and for the reasons stated in individual evaluations, the establishment of an acceptable daily intake expressed in numerical form is not deemed necessary. An additive meeting this criterion must be used within the bounds of good manufacturing practice, i.e., it should be technologically efficacious and should be used at the lowest level necessary to achieve this effect; it should not conceal inferior food quality or adulteration, and it should not create a nutritional imbalance.

The Cosmetic Ingredient Review Board (CIR)<sup>4</sup> undertook a review of methyl cellulose as one of several cellulose derivatives. The Scientific Panel published the results of its review of the literature and its risk assessment conclusion in 1986 (Cosmetic Ingredient Review (CIR) 1986).

While the CIR assessment focused on the intended use of methyl cellulose as a cosmetic applied to the skin, the scientific assessment considered all the available published literature and multiple toxicology endpoints to be assured not only of the safety of the intended cosmetic use, but of alternate applications as well.

The CIR risk assessment was published as: “Final Report on the Safety Assessment of Hydroxyethyl cellulose, Hydroxypropyl cellulose, Methyl cellulose, Hydroxypropyl Methyl cellulose, and Cellulose Gum” in the Journal of the American College of Toxicology, Volume 5, Number 3, 1986. The abstract states:

Hydroxyethyl cellulose, Hydroxypropyl cellulose, Methyl cellulose, Hydroxypropyl Methyl cellulose, and Cellulose Gum are modified cellulose polymers that are used in cosmetic products at concentrations up to 10%. The cellulose derivatives pass essentially unchanged through the gastrointestinal tract following oral administration. They are practically nontoxic when administered by inhalation or by oral, intraperitoneal, subcutaneous or dermal routes. Subchronic and chronic oral studies indicate that the cellulose derivatives are nontoxic when administered to laboratory animals. No significant teratogenic or reproductive effects have been demonstrated. Ocular and dermal irritation studies show that cellulose derivatives are, at most, minimally irritating to rabbit eyes and non-irritating to slightly irritating to rabbit skin when tested at concentrations up to 100%. No mutagenic activity of these ingredients was demonstrated. The cellulose derivatives at concentrations up to 100% were non-irritating to mildly irritating, non-sensitizing, and non-

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<sup>4</sup> The Cosmetic Ingredient Review Board (CIR)<sup>4</sup> was established in 1976 by the Cosmetic, Toiletry & Fragrance Association\* (CTFA) with support of the US FDA and the Consumer Federation of America. Although funded by CTFA, CIR and the review process are independent from CTFA and the cosmetics industry. CIR thoroughly reviews and assesses the safety of ingredients used in cosmetics in an open, unbiased, and expert manner and publishes the results in open, peer-reviewed scientific literature.

photosensitizing when evaluated in clinical studies. It is concluded that the ingredients reviewed are safe as cosmetic ingredients in the present practices of use and concentration.

Methyl cellulose is broadly used as a direct human food additive for viscosity modification, thickening, film forming, stabilisation and thermal gelation. It is also broadly used as a pharmaceutical excipient as well as uses in the industrial and construction applications and in personal care applications. Dow's methyl cellulose meets specifications/purity criteria from Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2003) and for the EU food additives E 461 (European Commission 2008). Methyl cellulose is recognized as GRAS under U.S. FDA 21 CFR 182.1480 – Generally Recognized As Safe when used in accordance with good manufacturing practices. It is also approved as food additive E461 for use in foodstuffs at *quantum satis* (European Commission 1995).

A detailed toxicology summary of the publicly available literature on methyl cellulose toxicology testing is outlined below. Substitution ranges and viscosities have been indicated where possible to show that there are no toxicological differences observed with the different substitution ranges or viscosities of methyl cellulose. Also Appendix G provides a summary table of relevant toxicology endpoints.

## 11.1.2 Pharmacokinetics & Metabolism

### 11.1.2.1 Methyl Cellulose

**Human studies:** Methyl cellulose was administered to 23 male and two female human subjects. Each individual was given three graduated doses of methyl cellulose from 0.6 to 8.9 grams with a one week interval between doses. Essentially, the entire methyl cellulose ingested was recovered in the faeces 96 hours post-administration (Knight et al., 1952).

**Animal studies:** The disposition of orally administered radio-labelled methyl cellulose was measured in six rats given a single oral dose of 500 mg/kg bw/day. Another group of six rats received daily doses of methyl cellulose for five days. During the 48 hour period following administration of the single dose, 102.2% of the total dose of radio-labelled activity was eliminated in the faeces. No radioactivity was detected in the respired air. Less than 0.1% of the original dose was found in the urine, selected tissues and remaining carcass. No accumulation of radio-labelled activity was detected in the body or in selected tissues after multiple dosing. It was concluded that following oral administration to rats, high-viscosity methyl cellulose is not absorbed and is rapidly cleared through the body via the faeces (Braun, W.H., et al., 1974).

## **Analogues**

**Animal studies:** A similar disposition of <sup>14</sup>C-hydroxyethyl cellulose as noted for hydroxyl propyl methyl cellulose (HPMC) in male and female CDF (Caesarean derived Fisher) rats (Sullivan et al., 1968a) and in male and female CDF rats and dogs (sex and strain not reported) (Sullivan et al., 1968b). The pharmacokinetics and potential metabolism of HPMC have been evaluated in rats using <sup>14</sup>C-HPMC. Male and female Sprague-Dawley rats were administered 500mg of <sup>14</sup>C-HPMC as single or repeated bolus doses. In the single dose study, greater than 99% of the administered <sup>14</sup>C was excreted via the faeces, approximately 1% in the urine, and 0.3% in the carcass and tissues 72 hours after dosing. In the repeat dose study, animals were given five daily doses of <sup>14</sup>C-HPMC. Approximately 97 and 102% of the administered <sup>14</sup>C was excreted in the faeces in male and female rats, respectively and approximately 1% of the radioactivity was excreted in the urine. Radioactivity in carcass and tissues, absent the gastro-intestinal tract, was minimal and similar between males and females in both acute and repeat dose studies. There was no evidence of any tissue accumulation (Gorzinski et al., 1986).

### **11.1.3 Acute Oral Toxicity**

#### **11.1.3.1 Methyl Cellulose**

**Human studies:** Single oral doses of 5 and 10 grams of methyl cellulose taken as a 5% solution were well tolerated in man. More specifically, two male adults and one ten years old girl were given a dose of methyl cellulose at 10 different times. Faecal collection and analysis were done 1 to 4 weeks after dosing. All dosing was single acute oral dose (Machle 1944). Single doses of 0.6 to 8.9 grams of methyl cellulose were administered to 25 normal healthy young adults (23 male and 2 female). Methyl cellulose was given orally once a week for three weeks. Adults with only mild laxative or constipating effects were reported which may be due to its effects as a bulking laxative. Methyl cellulose was not absorbed to any significant extent with essentially all of it eliminated in 96 hours (Knight et al. 1952).

#### **11.1.3.2 Analogues**

**Animal studies:** A number of acute oral toxicity studies on modified cellulose derivatives have also demonstrated low oral toxicity of this family of compounds. Oral LD<sub>50</sub> values in rats (sex and strain not reported) for hydroxypropyl cellulose of 10,200-15,000 mg/kg/day (IBL, 1964; Kitagawa et al., 1976a), hydroxypropyl methyl cellulose of greater than 1000 mg/kg and greater than 4000 mg/kg (CFTA, 1978a, Hodge et al., 1950), ethylhydroxyethyl cellulose of 5000-10,000 mg/kg/day (Cuthbert et al., 1975), and ethyl cellulose of 5000 mg/kg/day (Moreno, 1977) have been reported.

## 11.1.4 Acute Toxicity, Other Routes

### 11.1.4.1 Methyl Cellulose

Whilst there are published studies on the effects of methyl cellulose via different routes of exposure, these routes are considered irrelevant for the assessment and are presented here for information only.

**Animal studies:** Acute toxicity was investigated in mice given a single intra-peritoneal injection of 147 mg/kg as a 5% solution of methyl cellulose. No lethal effects were reported at this dose level. An ED<sub>0</sub> was reported in mice administered 1.0 mg/kg of a 5% solution methyl cellulose (Informatics, 1972). Effects observed in dogs receiving a single intravenous injection of 40 ml of a 0.7% - 2.8% solutions in saline included anaemia, leucopenia and increased sedimentation rate. Methyl cellulose also accumulated in the liver, spleen, kidneys and vasculature walls (Heuper, 1944). "Rabbits injected intravenously with 10 mg/kg methyl cellulose developed leucopenia. However, injections of 10-100 mg/kg of 1% methyl cellulose solution had no effect on blood pressure or respiration (Weidersheim et al., 1953).

Intravenous injections, twice weekly with 20 mL of a 1% solution of methyl cellulose in rabbits induced sub-intimal deposits of methyl cellulose at arterial walls followed by extensive calcification, ossification, cartilage formation and lipid deposition (Stehben and Silver, 1966).

### 11.1.4.2 Analogues

**Animal studies:** Acute dermal toxicity of ethyl cellulose was evaluated in rabbits (Moreno, 1977). The LD<sub>50</sub> was reported to be greater than 5000 mg/kg/day.

**Human studies:** Dermal irritancy of hydroxypropyl cellulose has also been evaluated in human subjects (Cosmetic, Toiletry, and Fragrance Association (CFTA), 1962). Repeated application of a 10% aqueous solution of hydroxypropyl cellulose to the backs of 50 subjects for 24 hours did not elicit any signs of irritancy following a total of 10 exposures. A subsequent challenge dose several weeks following the latter dosing period failed to elicit an allergic response.

**Animal studies:** No mortality was observed in two rabbits following application of dry or moistened hydroxypropyl methyl cellulose to skin in a dermal irritancy study (Cosmetic, Toiletry, and Fragrance Association (CFTA) 1978b). In the latter studies no evidence of dermal irritation was noted with dry HPMC and only slight erythema was noted with moistened HPMC. The latter was attributed to sticking to the skin rather than a primary irritancy.

## 11.1.5 Allergenicity

### 11.1.5.1 Methyl Cellulose

**Human Studies:** Food allergy is an immune response in sensitised individuals to certain dietary proteins. Methyl cellulose is a substituted polysaccharide and therefore no proteins are present in the product. Since methyl cellulose is widely used in the food industry, an analysis was conducted on food grade methyl cellulose (Methocel A4M) to verify that no proteins (soy, milk, nut, etc.) are present as a potential source of allergens. Samples were analyzed using the Antek Total Nitrogen Chemiluminescence Analyzer for nitrogen as a presumptive test for protein. No nitrogen was detected down to the limit of quantification of 1 ppm. Therefore, methyl cellulose is not considered to have allergenic potential (Lewis, 2004). There are no known intolerances to cellulosic products.

### 11.1.5.2 Analogues

**Animal studies:** Hydroxy propyl methyl cellulose (HPMC) was evaluated for its potential as a skin sensitizer using the Magnusson-Kligman guinea pig maximization test (GPMT) and a modified Maguire method. The GPMT induction phase included 0.1 ml of 1% HPMC and 0.1 ml of 1% HPMC in 50% adjuvant. The challenge consisted of a 24 hours occlusive challenge patch with 25% HPMC. HPMC did not produce a sensitization response (CIR, 1986). Similarly, the test using the modified Maguire method failed to induce skin sensitization (CIR 1986). A more recent guinea pig maximization test was conducted on hydrophobically modified HPMC. Again, there was no indication of skin sensitization under the conditions of the test (Obara et al. 1998).

## 11.1.6 Sub-chronic Toxicity

### 11.1.6.1 Methyl Cellulose

Numerous short-term and sub-chronic toxicity studies of methyl cellulose in several species of test animals have been undertaken.

**Animal studies:** A dietary study was conducted in 80 rats given methyl cellulose (1500 cP) daily in their food and water up to 1% over a period of eight months. Food and water consumption and weight gain were not statistically different between treatment and control groups. A representative number of animals were killed and examined for any gross or microscopic changes in the tissues (not specified). No significant abnormalities were noted in any of the animals. The authors concluded that methyl cellulose in the diet at this level was harmless to rats (Deichmann and Witherup, 1943).

A 95 day dietary study in 10 male and 10 female rats fed up to 10% methyl cellulose (1400 cP) daily failed to demonstrate any significant findings. Organ weights, gross pathology and microscopic examination of tissues were normal (Tainter, 1943).

Rats fed a diet of 5% methyl cellulose (690 – 775 mg/kg bw/day) for thirty-two weeks demonstrated no change in dietary intake, growth, reproduction or tissue morphology. A subsequent experiment where a daily dose was delivered by supplementing the diet with 50% methyl cellulose, significantly depressed growth due to lack of nutrient intake. This effect was diminished when the rats were returned to a standard diet (Bauer and Lehman, 1951).

Groups of 10 male and 10 female young rats were fed diets containing methyl cellulose with a viscosity of 10 cP (0, 1, 3, and 10%) or a viscosity of 4000 cP (0.3 and 10%) for 90 days. Male rats consuming 10% methyl cellulose (viscosity of 10 cP) exhibited slight reductions in terminal body weight relative to controls but growth was normal in all other 10 cP treatment groups, and in all rats consuming the 4000 cP methyl cellulose. No significant treatment related effect was observed on other toxicological parameters examined in the study including serum chemistry, haematology, urinalyses, organ weights and pathology (gross and microscopic) (McCollister et al., 1973).

Finally, providing two dogs (sex and strain not reported) up to 100 grams of methyl cellulose daily for four weeks reportedly caused no adverse effects (Bauer, 1945).

#### 11.1.6.2 Analogues

**Animal studies:** The toxicity of hydroxypropyl cellulose has also been evaluated. Ingestion by rats (sex and strain not reported) of up to approximately 5000 mg/kg bw/day via the diet for 90 days resulted in no untoward effects (Industrial Biotest Lab, 1964). The only effect was an increase in feed consumption in high dose animals. In a 6-month dietary toxicity study of hydroxypropyl cellulose, the only treatment-related effect noted was a decreased haemoglobin level in rats fed 6000 mg/kg bw/day (Kitagawa et al., 1978b).

Ethylhydroxyethyl cellulose was evaluated in a 90-day dietary toxicity study in male and female CD rats (Elliot et al., 1985). The only treatment-related effect observed was an increase in liver weights of ingesting the high dose level of 2500 mg/kg bw/day; however, this was not accompanied by histopathological changes in liver tissues.

Chronic studies in rats, dogs and rabbits fed HPMC in varying viscosities and up to 30% supplementation in the diet failed to demonstrate any histopathic changes. The only significant effect observed in animal studies was a reduction of body weight at 9.6% and 20% supplementation in the diets of

dogs and rats, respectively (Obara et al. 1999; Mitchell, 1967). In rabbits, no adverse findings were attributable to HPMC up to 25% supplementation in the diet (Hodge, 1950). In rats an increase in mortality was observed at greater than 20% in the diet. (McCollister et al. 1961; McCollister and Oyen, 1954).

Toxicity studies of HPMC of widely varying viscosities conducted in dogs have also failed to identify any significant treatment related effects. Hodge et al. (1950) daily administered HPMC having a higher gel point by 10-15 °C than former methyl celluloses to dogs (sex and strain not specified) at up to 25% in the diet for 30 days resulting in diarrhoea and minor decreases in body weights. Administration of up to 3000 mg/kg/day of the same test material to dogs daily for a year produced no observable effects following a relatively comprehensive evaluation, including histopathology. Mitchell (1967) provided male and female Beagle dogs with up to 9.6% HPMC (50,000 cps) daily in the diet for 94 days and observed decreases in body weight gains at the high dose level only. No treatment-related effects were observed at 3.2% in the diet. McCollister et al. (1973), and Schwetz et al. (1973) found no effects on male and female Beagle dogs daily consuming diets containing up to 5% and 6% of lower viscosity HPMCs (4.22 cps and 10 cps, respectively).

### 11.1.7 Chronic/Carcinogenicity Studies

#### 11.1.7.1 Methyl Cellulose

**Animal studies:** Chronic dietary studies have been conducted with methyl cellulose in rats. Groups of 30 male and female rats were fed for two years on diets containing 0.1 or 5% of methyl cellulose of viscosity 15, 400, 4000 cP for two years. Gross pathological examinations were conducted on terminally ill rats or rats dying during the study, and on remaining survivors at termination. During necropsy, sections of grossly visible nodules or masses were preserved for histopathological examination. There was no indication of increased tumour incidence in rats receiving the methyl cellulose diets (McCollister et al., 1973).

Groups of 20 male and 20 female rats were fed chow diets containing 0.1% or 5% methyl cellulose of viscosity 15, 400, 4000 cP for two years. At termination, gross pathological examinations were performed and blood was sampled for hematologic evaluations and serum chemistry. Additional groups of 10 male and 10 female rats for each dietary level were interim sacrificed at 12 and 18 months and subjected to either gross pathologic examination or tested for haematology and serum chemistry parameters. During necropsy, selected tissues were weighed and preserved histopathological evaluation. No treatment-related effect was reported on mortality or any other test parameters over the course of the study (McCollister et al., 1973).

### 11.1.7.2 Analogues

**Animal studies:** Chronic dietary studies have been conducted in rats and dogs with various substituted celluloses. Hydroxyethyl cellulose was administered daily in the diet up to 5% for two years. While food intake increased in the high dose group, there were no other significant treatment related effects (Smyth et al., 1947). Hydroxypropyl methyl cellulose was fed to rats up to 25% of their diet for one year. No toxic effects were noted except for growth retardation in the 20 and 25% groups which may be attributed to the non-nutritive bulk content of the diet. Dogs fed hydroxypropyl methyl cellulose up to 50 g/day showed no treatment related effects as judged by urinalysis, haematologic examinations, gross and histological examinations of specified tissues (Hodge et al., 1950).

Methylethyl cellulose was fed to mice and rats at 0, 0.1, 1.0% of the diet for two years. There were no treatment related effects on survival, tumour incidence, haematology, gross and microscopic examination of organs (Imperial Chemical Industries, 1961). Carboxymethyl cellulose was tested in rats and mice (50 animals/sex/group) for 103 weeks at doses of 5 mg/kg for the rat and 50 mg/kg for the mouse via oral gavage. There was no difference in tumour incidence between the treated and control animals (National Cancer Institute, 1979). Studies in rats and mice (50 animals/sex/group) with up to 1% carboxymethyl cellulose in the diet for up to two years did not increase mortality or tumour incidence compared to controls (Imperial Chemical Industries, 1966; McElligot and Hurst, 1968). In a multi-generational study with rats treated up to 1000 mg/kg bw/day for two years, there were no treatment related effects according to growth rate, urinalysis, haematology, fertility and histopathology of major organs (Shelanski and Clark, 1948).

### 11.1.8 Genotoxicity

#### 11.1.8.1 Methyl Cellulose

**Animal studies:** Methyl cellulose has been tested in two in vitro bacterial reverse mutation (Ames) assays. Methyl cellulose at 50 ug/plate produced negative results using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 with and without metabolic activation (Blevins and Taylor, 1982). A similar study with methyl cellulose at concentrations up to 70 mg/plate demonstrated no mutagenic activity in strains TA92, TA94, TA98, TA100, TA1535, and TA1537 (Ishidate et al., 1984). An in vitro chromosomal aberration test was carried out using a Chinese hamster lung (CHL) fibroblast cell line. At concentrations up to 4.0 mg/ml, there was no increase in the number of structure aberrations 48 hours after treatment (Ishidate et al., 1984).



Further in vitro and in vivo studies have been cited in the literature. The Tenth Report of the Cosmetic Ingredient Review Expert Panel (1986) relates the following information:

“MC (methyl cellulose) was evaluated for mutagenicity in three different test systems: a host mediated assay (in vitro and in vivo). In the host mediated assay, no significant increase in mutant or recombinant frequencies was observed when methyl cellulose was tested in vitro at concentrations of 10% of in vivo at doses up to 500mg/kg (in mice) using *S. typhimurium* strain TA1530 and G-46 and *Saccharomyces* D3, respectively. In the cytogenetic studies, rats administered orally up to 5000 mg/kg methyl cellulose had no significant aberrations of the bone marrow metaphase chromosomes. No significant aberrations were noted in the anaphase chromosomes of human tissue cultures cells exposed up to 800 mcg/ml methyl cellulose. Methyl cellulose was non-mutagenic in the dominant lethal assay in rats dosed with up to 5000 mg/kg (Litton Bionetics, 1974).”

#### **11.1.8.2 Analogues**

HPMC has been directly evaluated in a Rat Bone Marrow Cytogenetics test. Chromosomal aberrations were not observed in rats ingesting a 5% diet of HPMC (USP 2910) for 90 days (Johnson et al., 1977). Extensive evaluations of analogues of HPMC have been undertaken and found to be negative.

#### **11.1.9 Reproductive & Developmental Toxicity**

##### **11.1.9.1 Methyl Cellulose**

**Animal studies:** Teratology studies have been conducted on hamsters, mice, rabbits and rats, pregnant mice (20-22 mice/group) administered daily gavage doses of methyl cellulose up to 1600 mg/kg bw/day during gestation day 6 to 15. On day 17, mice were sacrificed and subjected to Caesarean section and examination. Only at the highest dose was significant mortality observed and in survivors a decrease in pregnancy rates. There was an increase in resorption sites, a reduction in live foetuses which were retarded in maturation and weight. These effects are most likely secondary to the nutritional imbalance occurring in the dam given a very high fibre diet. There was no indication of any treatment related teratogenic effects (Food and Drug Research Laboratories Inc., 1973).

Similar studies in hamsters, rats and rabbits administered doses of methyl cellulose up to 1000, 1320, and 685 mg/kg bw/day, respectively, during the sensitive period of organogenesis for each species. In rats and hamsters the treatments had no clearly observable effect on nidation or on maternal or foetal survival. Rabbits in the high dose group of 685 mg/kg bw/day had an increased mortality rate in the dams and a decreased pregnancy rate in the

survivors. These effects are most likely secondary to the nutritional imbalance occurring in the dam given a very high fibre diet. The number of abnormalities seen in either soft or skeletal tissues on the test groups did not differ from those occurring in the controls (Food and Drug Research Laboratories, Inc., 1973).

Methyl cellulose has been tested for reproductive and developmental effects in mice and rats. Groups of 12-17 pregnant mice were administered methyl cellulose from gestation day (GD) 6 to 15 ranging from 70 mg/kg bw/day to 700 mg/kg bw/day. On GD 17 all surviving animals were sacrificed and submitted for caesarean section. No effects were observed on the number of implantations, live/dead foetuses, corpora lutea, resorptions or foetal weight (Cannon Labs 1975). There were no treatment related terata observed in this study.

A similar study was conducted in rats. Groups of 13-18 pregnant rats were administered methyl cellulose on gestation day 6 to 15. The doses ranged from 120 to 1200 mg/kg bw/day. On GD 20 all animals were sacrificed and submitted for caesarean section. No effects were observed on any reproductive index or terata with the exception of extra centers of ossification in the vertebrae in the high dose group (Cannon Labs., 1977).

There have been no reports of direct, treatment-related effects upon reproductive organs of males or females of several species of test animals in toxicity studies of sub-chronic duration or longer. This conclusion is consistent with that of the Select Committee on GRAS Substances who concluded at the time "There is no evidence in the available information on methyl cellulose that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when it is used at levels that are now current and in the manner now practiced" (FASEB, 1973).

#### **11.1.9.2 Analogues**

**Animal studies:** Hydroxypropyl cellulose ("low substitution", assumed to be USP 2910 or 2208) was found to have no effect on the reproductive ability of the F1 offspring at dose levels as high as 5000 mg/kg bw/day in rats (strain unspecified) (Kitagawa et al., 1978a). Mean litter weights and pre-implantation loss were increased in rats and rabbits at the 5000 mg/kg bw/day dose level. Hydroxypropyl cellulose ("low substitution", assumed to be USP 2910 or 2208) was also found to have no effect in Himalayan rabbits at doses administered orally up to 5000 mg/kg bw/day (Kitagawa et al., 1978b).

## 11.1.10 Human Data

### 11.1.10.1 Methyl Cellulose

**Ingestion:** Data for methyl cellulose were gathered in several studies totalling more than 100 persons. Methyl cellulose was investigated for its use as a laxative in three healthy volunteers. Each volunteer ingested 10 g/day for 8 days resulting in doubled stool volume and frequency (Tainter, 1943). In a similar study, 29 patients suffering from acute and/or chronic constipation) were given 1 to 3 grams/day of methyl cellulose from 3 to 180 days of duration and another eight patients suffering from acute and/or chronic constipation were given 6 g/day of methyl cellulose from 4 to 240 days of duration. In the majority of cases, 1 to 6 grams of methyl cellulose was effective for the relief of chronic or acute constipation. Its prolonged use did not produce evidence of systemic changes or toxicity (Schweig, 1948). Bauer (1945) reported that 2.5 to 5.25g of methyl cellulose taken orally as gels in 250 ml of water had a tendency to be mildly constipating. No other details are given.

Case histories of a number of patients who had been given 2 grams/day of methyl cellulose to improve bowel function did not indicate any toxic effects (Bargen, 1949). In one case study, two patients with severe chronic, pre-existing conditions were given 60 to 90 mls of a methyl cellulose preparation (Cologel®) daily for 5 days. There is no mention of the exact formulation of Cologel in the paper. A review of Colegel preparations on the Web would indicate that the maximum amount of methyl cellulose in the preparation is likely to be 90 mg/kg.

These patients had a history of developing severe gastrointestinal distress, oedema, visual disturbances and neurological signs. During hospitalization when these symptoms abated, the patients were given a methyl cellulose preparation. Subsequently, these patients again developed generalized oedema, visual disturbances and neurological signs which abated within 72 hours after cessation of intake. Since Cologel® was available in formulations up to 90 mg/kg, it is estimated that the maximum amount per patient is approximately 8 grams of methyl cellulose per day. There was no firm conclusion as to the underlying metabolic defect present responsible for individuals' condition (Crane et al., 1969). Due to the pre-existing condition of these patients, the relevance of these case reports for this assessment is questionable.

Five healthy volunteers were given 250 mg/kg bw daily of methyl cellulose divided into three equal portions over 23 consecutive days. The intakes for methyl cellulose for all participants ranged between 21.25 and 17.75 g/day. The treatment was well tolerated and there were no adverse effects on allergic responses, haematology, serum biochemistry, and urinalysis (Eastwood et al., 1990).

Fifty healthy adults and 59 adults suffering from constipation were administered a bulk laxative containing 1, 2, or 4 grams of methyl cellulose (4000 cP). In healthy adults, 4 grams of methyl cellulose increased faecal frequency, faecal water and faecal solids. All concentrations of methyl cellulose resulted in a statistically significant increase faecal frequency, faecal water, and faecal solids in chronically constipated individuals. The study concluded that methyl cellulose in a daily dose as low as 1g is an effective laxative (Hamilton et al., 1988). The effects noted were the faecal frequency and weight. These effects are neither unexpected nor remarkable.

Several human trials have been conducted to determine the efficacy of methyl cellulose as a bulk forming fibre in diets for patients to relieve constipation and to determine its effects on hypercholesterolemia. In the first study, 538 patients with a prior history of chronic constipation were selected for the study. Out of the 538 patients, data were available for 409 patients and consisted of the following groups taking methyl cellulose for 10 days: 198 patients taking one tablespoon (2 grams) per day, 162 patients taking two tablespoons (4 grams) per day, and 49 patients taking 3 tablespoons (6 grams) per day. The amount of methyl cellulose ingested did not affect the efficacy levels for ease of passage, bowel frequency, or consistency. Eighty-three patients did not complete the 10 day study regime. Reasons for dropping out of the study included: early response to medication without need to continue therapy, lack of efficacy of medication, lack of compliance, loss to follow-up and self-limited side effects. The self-reported side effects included abdominal pain, bloating, esophagitis, constipation, cramps, flatulence, impaction and other minor complaints. These side effects may have been secondary to methyl cellulose therapy. The study was not conducted with a placebo control. After the course of the 10 day therapy, 61% of the patients were noted as having less constipation and in 57% of the patients methyl cellulose was rated more effective than other previously used laxatives (Snape, 1989).

In the second study, methyl cellulose was added to the diet of hypercholesterolemic patients to increase fibre intake and lower cholesterol. The 29 patients were given 1 tablespoon (2 g methyl cellulose) as Citrucel powder, three times per day before meals in at least 240 ml of water for eight weeks. No serious reactions occurred in any of the treatment groups. Five of the 29 subjects taking methyl cellulose reported symptoms including nausea, cramps, irregular bowel movements, constipation, intestinal gas, bloating, headaches or tiredness/achiness. The effects were comparable to the placebo group where 6 of the 31 subjects reported similar symptoms such as nausea, upset stomach, stomach cramps, diarrhoea, constipation, feeling bad/tired or leg aches (Anderson et al., 1991). The effects in the placebo group have been provided here for comparison.

**Sensitization and Irritation:** There was no information located on the skin sensitization by methyl cellulose. However, the Tenth Report of the Cosmetic Ingredient Review Expert Panel evaluated two studies where formulated

products containing 0.2% and 0.25% methyl cellulose were tested on human subjects for irritancy and sensitivity (CIR 1986). In 50 subjects, a shampoo containing 0.25% methyl cellulose was tested using a repeat insult patch test. The only reactions seen in the subjects were observed under occlusive conditions. In the 50 patients, primary irritation was observed in 11 subjects at induction and six subjects at challenge. The conclusion of the report indicated that this formulation containing methyl cellulose was capable of being an irritant but not a sensitizer (Cosmetic Ingredient Review, 1986). It is not possible to conclude if the irritation observed in the above study was caused by the 0.25% methyl cellulose or by another ingredient of the formulation.

### 11.1.10.2 Analogues

**Ingestion:** Human data have also been collected for ethylhydroxyethyl cellulose and hydroxylpropyl methyl cellulose. Ethylhydroxyethyl cellulose was administered in doses of 1.0-1.5g, three times daily, for at least two months to 85 male and female ambulatory patients (aged 21-75 years) with intestinal problems (Tomenus, 1957). Sixty-eight remained on treatment. X-ray contrast media were used to study tablet disintegration in several patients. Except for minor abdominal discomfort in some patients, no toxicity was noted and restoration to normal bowel movement was seen.

In a clinical human trial with mildly hypercholesterolemic patients, HPMC was given at different viscosities. Two trials were conducted: one with 12 patients taking a medium (3915 cP), high (22703 cP) and an ultra-high (63030 cP) viscosity HPMC at 15 g/day for one week and a second trial with 20 patients taking ultra-high viscosity HPMC at 5 g/day and 10 patients taking ultra-high HPMC at 15 g/day for eight weeks. The results of the study lowered LDL cholesterol with minor adverse effects (mild to moderate flatulence and mild bloating) (Reppas et al., 2009). Several formulations of HPMC were investigated for their lipid lowering effects. Groups of patients with primary hypercholesterolemia (approximately 15/group) were administered 3, 5, and 10 g/day of HPMC of varying viscosities: low, moderate, moderately high and high. Results indicated that HPMC is effective in reducing cholesterol in patients while being well tolerated. There were no statistically identified differences between treatments and controls for gastrointestinal related adverse effects (Maki et al., 2009).

In a similar study, Maki et al. (1999) administered up to 7.5 g/day HPMC to lower cholesterol. The study indicated that HPMC was effective in lowering LDL cholesterol and that there were no significant differences between the treatment and control groups with respect to any adverse experiences.

**Sensitization and Irritation:** The Tenth Report of the Cosmetic Ingredient Review Expert Panel evaluated approximately 24 human subject trials with different formulations of hydroxyl ethyl cellulose (HEC, 0.3% to 100%), hydroxypropyl methyl cellulose (HPMC, 1.1%), hydroxyl propyl cellulose

(HPC, 0.7% to 10%) and carboxymethyl cellulose (CMC, 0.605%). For HEC 15 studies were evaluated, overall the skin irritancy ranged from mildly irritating to essentially non-irritating and was a non-sensitizer. For HPC 7 studies were evaluated, only 3 subjects out of 424 studies showed a slight erythema. HPC was non-irritating and non-sensitizing. Only one study consisting of 25 subjects was evaluated for HPMC. Only a few irritant reactions were observed but were attributed to the drying effect of the product. No signs of sensitization were noted. No irritant or sensitization reactions were noted for carboxy methyl cellulose (CIR 1986).

## **11.2 Other Safety Considerations**

Two potential safety considerations were identified for Dow's methyl cellulose: (i) a choking risk, depending on the nature and extent of gel formation during swallowing (ii) an overdose hazard, should a user ingest a dose so large that the gel mass formed in the stomach could not be evacuated.

### **11.2.1 Choking Potential**

Using volunteers, Dow has assessed the potential for swallowing issues comparing samples at 4°C and at 20°C. No subjects reported any difficulties. Dow's methyl cellulose gels sufficiently slowly and the gel is sufficiently soft that choking is not seen as a significant risk. The gel feels similar to Jello™ brand gelatin except that under shear, it liquefies instead of fragmenting. Literature examples of choking with dietary fibres are not relevant in this case. A US FDA label requirement for choking with all dietary fibres was driven by early incidents with guar tablets which swelled on hydration in the mouth and throat. Konjac-Mannan, a natural soluble fiber used in candies in Asia which has been reported to cause choking in children, swells on gelation. Dow's methyl cellulose will be presented as a fully hydrated solution which does not swell on gelation (Anderson, 2009).

### **11.2.2 Overdose Hazard**

Mice were treated with a 3x normal dose of Dow's methyl cellulose. As expected the stomachs at one hour were significantly distended by solid gel masses. Significant clearance was observed after 2 hours which continued through subsequent time points. Clearance occurs by two processes. Particles of gel were observed in the intestine after two hours demonstrating that the stomach was able to break the initial mass into smaller pieces which could be excreted. Methyl cellulose gels also revert to liquid by dilution with available water resulting in clearance from the stomach (Anderson et al. 2010).

Due to its physical nature, Dow's methyl cellulose does not pose a significant choking or overdose hazard. The gel is relatively soft and can be broken by the shear forces in a mouse stomach. The gelling process is sufficiently slow, that significant gelation is not perceived to take place during swallowing. No difficulty in swallowing was encountered by any subject.

### **11.2.3 GI intolerance/laxation in susceptible children**

Methyl cellulose is well tolerated in humans given up to 6 g/day as a bolus dose. In a human study, mild to moderate gastrointestinal effects such as nausea or diarrhea, were comparable to an appropriate placebo control group (Anderson et al. 1991). Methyl cellulose, like other cellulose analogues, are resistance to fermentation in the colon and may reduce the gastrointestinal distress from gases formed during fermentation unlike other dietary fibres.

Fecal frequency and weight have been reported at doses of 1 g/day or higher (Schweig 1948). The effects do not seem to be related to viscosity grade of the product. For adults and children, we expect that the effects will be similar and comparable to an individual on high fibre intake. Such effects are neither unexpected nor remarkable and could be interpreted as a beneficial, rather than adverse, depending on the baseline situation among consumers.

### **11.3 Conclusion**

The toxicological studies indicate that methyl cellulose can be consumed by humans up to 6g/day 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.

## **12 Proposed labelling**

### ***How the novel food ingredient will be declared in an ingredient list?***

Dow's methyl cellulose is intended to be labelled in the ingredient list as methyl cellulose. It will contribute to the dietary fibre content of foodstuffs. Dietary fibre content will be declared on a food label via the nutritional table, as laid down in Directive 496/90/EEC on nutrition labelling (European Commission 1990).

Proposed alternative names are: Vegetal gel or fibrous plant gum or fibrous plant gel.

Dow's methylcellulose will be marketed under the Satisfit™ and METHOCEL™ trade name umbrella.

## **13 CONCLUSION**

The safety of methyl cellulose as a food additive (E461) has been reviewed in the EU. Dow's methyl cellulose ingredient is the same substance as E461 and meets the purity criteria set for E461 in Directive 2008/84/EC (as amended) (European Commission 2008).

Highest predicted intakes of methyl cellulose (97.5<sup>th</sup> percentile; consumers only) as a novel food ingredient based on a conservative deterministic approach are lower than the lowest plausible safety threshold of 6g/d, based on a human study, described in section 11.

When conservative (deterministic) baseline intakes of methyl cellulose as a food additive are taken into account, it is plausible that combined high level consumption (97.5<sup>th</sup> percentile among consumers only) may marginally exceed a threshold of 6g/d.

However, the conservative assumptions employed in both deterministic intake assessments, which assume that methyl cellulose is *always* present at a maximum fixed concentration in all foods and that *all* foods are consumed in high amounts, are very unlikely to be the case in practice.

For example, a snapshot of food additive usage in processed foods on the Irish market from the Irish National Food Ingredient Database showed that only 54% of additives permitted for use in the EU were used (Gilsenan et al., 2002). In addition, of the 5684 processed foods included in the food ingredient database (qualitative information collected from food labels), less than 0.1% recorded the use of methyl cellulose on their labels (FSAI, 2001). These data illustrate that actual usage of methyl cellulose as a food additive is considerably lower than the usage assumed in the above baseline intake estimates (i.e. 100% probability of presence). A more refined baseline intake assessment, employing a lower probability of presence, would inevitably yield considerably lower (baseline) intake estimates of methyl cellulose.

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 probabilistic intake estimates (97.5<sup>th</sup> percentile among consumers only) are lower than the plausible safety threshold of 6g/day. When baseline (probabilistic) intakes are taken into account, it is likely that combined high level intakes would still be lower than plausible safety threshold of 6g/day.

On the basis of the available toxicology 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.

The effects of methyl cellulose on GI intolerance and laxation are not expected to be different to those individuals consuming a high-fibre diet.



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## **15 APPENDICES**