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1001 G Street, N.W.  
Suite 500 West  
Washington, D.C. 20001  
tel. 202.434.4100  
fax 202.434.4646

September 20, 2006

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**Writer's Direct Access**

**Melvin S. Drozen, Esq.**  
(202) 434-4222  
drozen@khlaw.com

**Devon Wm. Hill, Esq.**  
(202) 434-4279  
hill@khlaw.com

***Via Federal Express***

Laura M. Tarantino, Ph.D.  
Food and Drug Administration  
Center for Food Safety and Applied Nutrition  
Office of Food Additive Safety, HFS-200  
University Station (CPK2)  
4300 River Road  
College Park, Maryland 20740-3835

**Re: GRAS Notification for Hydroxypropyl Methylcellulose**

Dear Dr. Tarantino:

Pursuant to proposed 21 C.F.R. § 170.36(c), on behalf of our client, the Dow Chemical Company, we hereby notify the Food and Drug Administration (FDA) of Dow's determination, on the basis of scientific procedures in accordance with 21 C.F.R. § 170.30, that the use of its hydroxypropyl methylcellulose (HPMC) product is generally recognized as safe (GRAS) when used in food for multiple technical effects, including as a source of dietary fiber. The enclosed Notification is a revised version of the GRAS Notice that was submitted by Dow Chemical Company on January 11, 2006 and subsequently withdrawn. The revised Notification addresses the additional information requested by FDA during our subsequent conversations with the Agency and our June 5, 2006 meeting with officials in the Office of Food Additive Safety.

In our opinion, HPMC is properly considered to be exempt from the definition of a food additive and the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act. Our conclusion is further supported by a review of this GRAS Notification by three well-known toxicologists, who have concurred with this GRAS determination. The reasons for Dow's GRAS conclusion regarding its HPMC product are discussed in detail in the company's GRAS Notification, which is enclosed in triplicate.

**KELLER AND HECKMAN LLP**

Laura M. Tarantino, Ph.D.  
September 20, 2006  
Page 2

We trust you will find the enclosed Notification acceptable. Should any questions arise during the review process, please do not hesitate to contact either of us, preferably by telephone, so that we may respond as quickly as possible.

Very truly yours,

Melvin S. Drozen

Devon Wm. Hill

Enclosures

cc: Mark Duvall, Esq.  
Imogene Treble, Ph.D.  
Maureen Kozuch

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**Notification of the Determination of**  
**Hydroxypropyl Methylcellulose (HPMC)**  
**As Being**  
**Generally Recognized As Safe**

Prepared by  
The Dow Chemical Company  
and submitted to the Food and Drug Administration

September 20, 2006

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## **Introduction**

The Dow Chemical Company (Dow) submits the enclosed dossier of information in support of this notification that hydroxypropyl methylcellulose (HPMC) is Generally Recognized as Safe (GRAS) for use in food, in accordance with good manufacturing practices (GMP), for multiple technical effects and as a dietary fiber in foods. The determination of GRAS status is on the basis of scientific procedures, in accordance with 21 CFR § 170.30(b) and conforms to the guidance issued by the Food and Drug Administration under *proposed* 21 CFR § 170.36, 62 Fed. Reg. 18938 (Apr. 17, 1997).

We submit information in the following areas:

- Identity of the substance, including recognition of HPMC in the Food Chemicals Codex and by the Joint FAO/WHO Expert Committee on Food Additives (JECFA).
- The production of HPMC as practiced by Dow.
- Analytical methodology, included by reference to the Food Chemicals Codex, and JECFA.
- An estimation of consumption of HPMC under new applications.
- Safety data, included by reference to two peer-reviewed expert publications and a thorough review of other published studies.
- Safety evaluation, supported by reference to the evaluations of two recognized evaluation bodies.
- GRAS determination, as a proposed conclusion determined by scientific procedures for use in food for multiple technical effects and as a dietary fiber in foods.
- External panel reviewers' evaluation and conclusion that HPMC is GRAS for its intended uses.

It is our expectation that FDA will concur that the information presented fully supports the determination of HPMC as produced by Dow is GRAS for use in food in general for multiple technical effects and as a dietary fiber in foods.

### **I. Administrative Information**

#### **1. Claim Regarding GRAS Status**

Dow hereby notifies the agency of its determination that HPMC is GRAS based on scientific procedures for use in food in general, for multiple technical effects and as a dietary fiber in foods and meat products for uses up to 20 grams/day.

#### **2. Name and Address of the Notifier**

Dr. Imogene Treble  
Environment Health & Safety Regulatory Leader  
The Dow Chemical Company  
171 River Road  
Piscataway, New Jersey 08854

### **3. Common or Usual Name of the Subject Substance**

Hydroxypropyl methylcellulose (HPMC)

Synonym:

Hypromellose

MHPC

Propylene Glycol Ether of Methylcellulose

Modified Cellulose

### **4. Conditions of Use/Applications**

HPMC offers a number of functions in various food categories. The properties of viscosity modification, thickening, film-forming, stabilization, and thermal gelation are used to enhance processed foods. HPMC is used as a direct human food additive. HPMC exerts these functional changes in food products without undergoing or initiating chemical changes that would alter the nutritional value of the food products.

### **5. Specific Jurisdiction Regulations**

HPMC is currently used as a food additive in many jurisdictions. There are current monographs for HPMC established by the Food Chemicals Codex (Fifth Edition), and JECFA.

### **6. History of Use in Food**

HPMC has a history of use in food dating back to 1952. Sales records for Dow indicate sales to food producers as far back as 1952 with use dramatically increasing in the mid-to late 1950's. In 1956, 1957 and 1958 the numbers of customers in the United States purchasing Dow's HPMC for use in food was 22, 23 and 26, respectively. FDA has approved HPMC for use in food as stated in 21 CFR § 172.874. HPMC has been commonly used in beverages, whipped toppings, pie fillings, toppings and dressings, glazes and ice cream since the late 1950's.

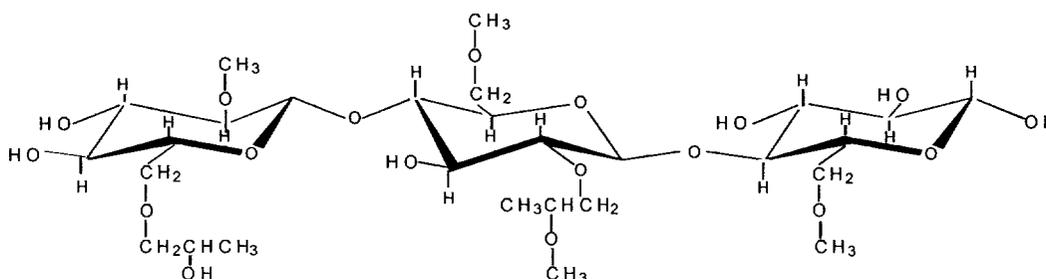
## II. Detailed Information about the Identity of the Notified Substance

### 1. Names and Other Identities

Chemical Name: Cellulose, 2-hydroxypropyl methylether  
CAS Registry Number: 9004-65-3  
Empirical Formula:  $[C_6H_7O_2(OH)_x(OCH_3)_y(OCH_2CHOHCH_3)_z]_n$   
where  
z = molar substitution of hydroxypropyl  
y = molar substitution of methoxy  
x = 3-(z + y): (z + y = degree of substitution)

Structural Formula:

## Hydroxypropylmethyl cellulose



Joint FAO/WHO Expert  
Committee on Food  
Additives name:

Hydroxypropylmethyl cellulose  
Defined as: A methyl cellulose modified with a small amount of 2-hydroxypropyl groups attached through ether links to anhydroglucose units of the cellulose. The article of commerce may be further specified by viscosity.

Food Chemicals Codex  
name:

Hydroxypropyl Methylcellulose  
Synonyms: Propylene Glycol Ether of Methylcellulose;  
Modified Cellulose; HPMC

PAFA Database Document  
Number:

710. The PAFA Database Number is maintained by the U.S. Food and Drug Administration (FDA) Center for Food Safety and Applied Nutrition (CFSAN) under the Priority-based Assessment of Food Additives (PAFA) program

European Pharmacopeia  
name and number:

Hypromellose 01/2002:0348

United States Pharmacopeia

Hypromellose, synonyms: hydroxypropyl methylcellulose,

name:  
Japanese Pharmacopeia      Hypromellose  
name:  
INS number:                    464  
Synonyms:                      Hypromellosum  
RTECS number:                NF9125000

**2. Substitution Range**

Methoxy (OCH <sub>3</sub> )	16 – 31.5%
Hydroxy Propyl (HP)	2 – 32%

**3. Specification**

**The following tests are conducted on an audit basis:**

Tables of lot analysis follow on the pages indicated below.

Solubility - Swelling in water, producing a clear to opalescent, viscous colloidal solution; insoluble in ethanol – Method – Current USP-NF Identity Test (Table A page 7)

Arsenic – Not more than 2 mg/kg – Method – JP <4> Method 3 (Table B page 8)

Lead – Not more than 3 mg/kg – ASTM D1976-91 (Table C page 8)

Heavy metals – Not more than 10 mg/kg – Method II <231> USP (Table D page 9)

**The following tests are conducted on each batch produced:**

See Table E page 9.

Assay – Determine the substituents by gas chromatography - Method – Current USP-NF Assay Test (Methoxy and Propyl % in Table E)

Loss on drying – Not more than 5% - Method <731> USP (Moisture in Table E)

pH – Not less than 5 and not more than 8 (1 in 100 soln) (pH in Table E)

Residue on ignition – Not more than 1.5% for products with viscosities of 50 centipoises or above, and not more than 3% for products with viscosities below 50 centipoises – Method <281> USP (Sulfated Ash in Table E)

**The following test is conducted on request:**

Propylene chlorohydrins – Not more than 0.1 mg/kg – JECFA – Propylene Chlorohydrin Test (See Possible Residuals discussion pg. 27)

Copies of the JECFA, FCC and USP HPMC monographs are included in Appendix A. Methods for the above specifications may be found in the attached monographs or the source document. Also included in Appendix A is the Arsenic Limit Test from JP XIV (Japanese Pharmacopeia). The substitution range given above is not the same as the ranges in the attached monographs, but the specification above was developed by using the most stringent endpoints from these monographs.

**4. Analysis of Lots of HPMC**

Analysis of various lots of HPMC food grade products are shown below.

The USP –NF Identity test includes three different identity tests (A,B,C) which are described in the USP-NF Monograph. These tests are performed annually.

**Table A - USP-NF Identity Test**

Sample ID	Test	Specifications	Results	Status
SF18012N21	Identification A	The mixture remains stable when an equal volume of 1N Sodium Hydroxide or 1N Hydrochloric Acid is added.	Meets specifications	Conforms
SF18012N21	Identification B	The slurry is formed, but the powdered material does not dissolve; the resulting liquid is clear or opalescent mucilaginous colloidal mixture.	Meets specifications	Conforms
SF18012N21	Identification C	A thin, self-sustaining film results.	Meets specifications	Conforms
TD07012N11	Identification A	The mixture remains stable when an equal volume of 1N Sodium Hydroxide or 1N Hydrochloric Acid is added	Meets specifications	Conforms
TD07012N11	Identification B	A slurry is formed, when cooled to 20degC, the resulting liquid is a clear or opalescent mucilaginous colloidal mixture	Meets specifications	Conforms
TD07012N11	Identification C	Thin self-sustaining film results	Meets specifications	Conforms

**Table B - Arsenic**

<b>Sample ID</b>	<b>Client Specifications</b>	<b>Results</b>	<b>Status</b>
TA07012N15	NMT 2 ppm	<2 ppm	Conforms
TK28012N11	NMT 2 ppm	<2 ppm	Conforms
UB15012N32	NMT 2 ppm	<2 ppm	Conforms
TG24012N31	NMT 2 ppm	<2 ppm	Conforms
UC16012N12	NMT 2 ppm	<2 ppm	Conforms

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**Table C - Lead**

<b>Sample ID</b>	<b>Specifications</b>	<b>Results</b>	<b>Status</b>
TC24012N22	NMT 3 ppm	<3 ppm	Conforms
TL16012N22	NMT 3 ppm	<3 ppm	Conforms
TC24012N22	NMT 3 ppm	<3 ppm	Conforms
TL16012N22	NMT 3 ppm	<3 ppm	Conforms
SA25012N11	NMT 3 ppm	<3 ppm	Conforms
SG30012N02	NMT 3 ppm	<3 ppm	Conforms

**Table D - Heavy Metals**

<b>Sample ID</b>	<b>Specifications</b>	<b>Results</b>	<b>Status</b>
TB25012N12	NMT 0.001%	<0.001%	Conforms
TD19012N11	NMT 0.001%	<0.001%	Conforms
TH11012N21	NMT 0.001%	<0.001%	Conforms
TK28012N11	NMT 0.001%	<0.001%	Conforms
UB20012N01	NMT 0.001%	<0.001%	Conforms
UA27012N11	NMT 0.001%	<0.001%	Conforms
UD12012N22	NMT 0.001%	<0.001%	Conforms

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**Table E - Batch Analysis of 5 lots of HPMC Food Grade Product**

**Analysis of Representative Batches of USP 2208**

<b>Batch Name</b>	<b>Methoxy</b>	<b>Propyl</b>	<b>Moisture</b>	<b>pH</b>	<b>Sulfated ash</b>
UA03012N13	22.7	8.6	2.3	6.1	0.6
UA04012N11	22.7	8.4	2.0	5.8	0.6
UA04012N12	22.7	8.5	2.5	6.0	0.4
UA05012N11	23.1	8.9	2.0	5.8	0.5
UA14012N12	23.1	8.8	1.6	6.0	0.5

**5. Physical Description:** white/off-white powder

**6. Method of Manufacture**

The important raw materials for the manufacture of HPMC are as follows: pulp (cellulose), methyl chloride, propylene oxide, caustic soda solution, acid, buffering agent,

and water. The raw materials are of a purity and quality suitable for their intended use. No raw materials from animal sources are used. All raw materials have written raw material specifications that include test methods. Each shipment of raw materials is evaluated by internal quality control standards to assure conformation with the specifications.

HPMC has a polymeric backbone of cellulose, a natural carbohydrate that contains a basic repeating structure of anhydroglucose units. During the manufacture of HPMC, cellulose fibers are heated with a caustic solution, which in turn is treated with methyl chloride and propylene oxide. The fibrous reaction product is purified and ground to a fine, uniform powder.

For HPMC products, propylene oxide is used in addition to methyl chloride to obtain hydroxypropyl substitution on the anhydroglucose units. This substituent group,  $-OCH_2CH(OH)CH_3-$ , contains a secondary hydroxyl on the number two carbon and also may be considered to form a propylene glycol ether of cellulose. These products possess varying ratios of hydroxypropyl and methyl substitution, a factor which influences organic solubility and the thermal gelation temperature of aqueous solutions.

See Appendix B for a process flow diagram which details the scheme for the production of HPMC.

Good manufacturing practices (GMP) for the production of HPMC are followed.

## 7. Product Description

HPMC is formulated as a powder and has the following typical composition:

Hydroxypropyl methylcellulose	85-99%
Water	1-10%
Sodium Chloride	0.5-5%

Each HPMC product produced has a specification. Not all products require the exact same list of test methods, nor do all products have the same limits for each variable tested. Typical products currently produced are those defined by the current FCC and USP-NF substitution ranges. Dow anticipates that other substitution ranges may provide unique additional properties that may be beneficial in future food applications. Variations in the substitution ranges of HPMC impact the process performance in processed foods. Thus, the broadened substitution range is expected to result in products with improved properties for stabilization, air entrainment and gel formation in foods.

The types of variables and the limits are very product and customer specific. Quality control utilizes the test methods as written by the USP or an equivalent test or Dow method that has been statistically validated.

HPMC is known to be a stable substance. HPMC is known to pick up moisture from the air in storage. High-viscosity grades of HPMC may demonstrate some loss of viscosity after long storage.

HPMC, like many other polysaccharides, will start to degrade rather than exhibit melting behavior. Specifically, HPMC will brown at 190 - 200°C, char at 225 - 230°C, and burn out between 260° and 300°C. However, HPMC has very good thermal stability at lower temperatures. An untreated HPMC product can usually withstand 100°C for several hours without degradation or loss of effectiveness.

Regardless of pH, HPMC solutions (like all cellulose ethers) are not stable in the presence of oxidizing agents such as bleach (sodium hypochlorite) or hydrogen peroxide. The instability is observed as a loss in viscosity.

## **8. Properties of the product**

Quality – The quality of HPMC is assured by the well-known and understood manufacturing process. When GMPs are applied, the level of control of the process will assure the purity of the product. The test requirements of the Food Chemicals Codex monograph and the JECFA monograph provide excellent assurance of the identity, and purity of HPMC for use in foods. HPMC is also produced under GMPs as an excipient for pharmaceutical applications.

Efficacy – HPMC is demonstrated to provide desired functional effects in processed foods at low concentrations. These functional effects will not conceal inferior food quality or adulteration, nor create a nutritional imbalance. The test requirements of the Food Chemicals Codex monograph and the JECFA monograph provide excellent assurance of the efficacy of HPMC for use in foods.

## **III. Detailed Summary of the Basis for Notifier's GRAS Determination**

### **1. Dietary Exposure and Applications**

#### **a. Dietary Exposure**

The level of use of HPMC is expected to be self limiting. General use in food of up to 20 grams/day would be generally recognized as safe. Effects that can occur when the upper limits of HPMC in foods are exceeded are: undesirable mouth feel, undesirable texture, and off flavor. These technical effects control the upper limits of HPMC that are able to be used in food and are, therefore, self limiting. This includes both low viscosity and high viscosity products. Low viscosity products are defined as being less than 1500 centipoise and high viscosity products are defined as being greater than or equal to 1500 centipoise. This self-limiting effect generally occurs at HPMC levels of 2-5% depending on the specific food and the HPMC viscosity. Examples of some potential uses would be: white breads, breakfast cereals, pasta, tortillas, cakes, cookies, biscuits, and granola

bars, fruit juices, fish sticks, frozen dinners and canned pastas, omelets and egg white substitutes, veggie burgers and meat substitutes, peanut butter, sugar substitutes, candy bars and fruit roll-up type snacks.

There is also the potential for use of HPMC as a dietary fiber. *Dietary Guidelines for Americans* is published jointly every 5 years by the Department of Health and Human Services (HHS) and the Department of Agriculture (USDA). Fiber recommendations contained in the guidelines recommend a range of 19 to 38 grams of fiber a day depending on the age and gender of the individual.

## **2. Safety of Use in Foods**

### **a. Safety Evaluations**

This GRAS determination is based in part on published reviews of HPMC safety. Described below are two comprehensive reviews of available toxicology literature and the conclusions of the World Health Organization (WHO) and Cosmetic Ingredient Review (CIR).

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) is an international expert scientific committee that is administered jointly by the Food and Agriculture Organization of the United Nations (FAO) and WHO. It has been meeting since 1956, initially to evaluate the safety of food additives. Its work now also includes the evaluation of contaminants, naturally occurring toxicants and residues of veterinary drugs in food. The Committee has developed principles for the safety assessment of chemicals in food that are consistent with current thinking on risk assessment and take account of recent developments in toxicology and other relevant sciences. The JECFA review of the literature on HPMC, and its risk assessment conclusion, was published in 1990.

HPMC was independently and thoroughly 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 35<sup>th</sup> meeting. A Group ADI of "not specified" for modified celluloses established at the thirty-fifth meeting (1989): ethyl cellulose, ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose, methyl ethyl cellulose, and sodium carboxymethyl cellulose; cross-linked sodium carboxymethyl cellulose added at the fifty-ninth meeting (2002). [See, WHO Food Additive Series No. 26-JECFA 35/81 (1989).] 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 toxicological literature on all substitutions and viscosities of HPMC and other modified celluloses, as discussed below, supports this interpretation of the data.

The evaluation of HPMC by JECFA is that the acceptable daily intake (ADI) is “not specified”. 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 diarrhea 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 fiber in general.” JECFA further explains the estimate of ADI as “not specified”:

This term 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.

CIR was established in 1976 by the Cosmetic, Toiletry & Fragrance Association (CTFA) with support of 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 the open, peer-reviewed scientific literature. CIR undertook a review of HPMC 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.

While the CIR assessment is focused on the intended use of HPMC 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 too.

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

Hydroxyethylcellulose, Hydroxypropylcellulose, Methylcellulose, Hydroxypropyl Methylcellulose, 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 the cellulose derivatives are, at most, minimally irritating to rabbit eyes and nonirritating 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 nonirritating to mildly irritating, nonsensitizing, and nonphotosensitizing 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.

#### **b. Toxicology Summary**

As described in the toxicology summary below, the substitution range defined in this notification is supported by the scientific literature. There have been no toxicological differences observed when HPMC with different substitution ratios have been tested. In addition, the lack of toxic effects extends to other derivatized cellulose products including methyl cellulose (GRAS listing at 21 CFR § 182.1480) and sodium carboxymethyl cellulose (GRAS listing at 21 CFR § 182.1745). This is due primarily to the fact that these large molecular weight ingredients are not significantly absorbed from the gastrointestinal system.

The toxicology of the class of modified cellulose, and HPMC specifically, is determined by the absence of absorption from the gastrointestinal system and, therefore, the absence of systemic bioavailability. The data are consistent among all cellulose types, including unmodified celluloses, all molecular weights and viscosities, and all types of modifications, including crosslinking: no frank toxic effects were observed, except at feeding levels that interfered with the ability of test animals to consume adequate nutrients and calories. In subchronic and chronic studies with HPMC in dogs, consumption of approximately 36 grams per day and 54 grams per day showed no effects. These observations are consistent with the chemical inertness of the ingredient class. The absence of toxicological effects encompasses acute, subchronic, chronic exposures; developmental and reproductive effects, and genetic toxicity. The consumption of large amounts of celluloses or modified celluloses by humans has substantiated the absence of harm. Human subjects consumed large amounts of all types of celluloses without adverse effect over short periods of time.

A detailed summary of the publicly available literature on HPMC toxicology testing is 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 HPMC. Also attached is a table of relevant toxicology endpoints. A bibliography of all studies can be found in Appendix D, and copies of all studies are available for review by FDA if needed. Superscripts below refer to studies listed in Appendix D.

#### **Acute Oral Toxicity**

### ***HPMC***

The acute oral toxicity for HPMC has been evaluated in two studies. LD<sub>50</sub> values in rats (unspecified strain and sex) of greater than 1000 mg/kg/day (CTFA, 1978a) and greater than 4000 mg/kg/day in adult fasted rats (<sup>2</sup>Hodge *et al.*, 1950) were reported.

### ***Analogues***

A number of acute oral toxicity studies on modified cellulose derivatives have also demonstrated the relatively 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 (<sup>12</sup>IBL, 1964; <sup>13</sup>Kitagawa *et al.*, 1976a), ethylhydroxyethyl cellulose of 5000-10,000 mg/kg/day (<sup>17</sup>Cuthbert *et al.*, 1975), and ethyl cellulose of 5000 mg/kg/day (<sup>47</sup>Moreno, 1977) have been reported.

## **Acute Toxicity, Other Routes**

### ***HPMC***

The acute toxicity of HPMC in male albino rats and albino mice (sex not reported) has also been evaluated via an intraperitoneal route of administration. The LD<sub>50</sub> values were reported by <sup>2</sup>Hodge *et al.* (1950) to be 5000 mg/kg/day in each species. In addition, no mortality was observed in two rabbits (sex and strain not reported) following application of dry or moistened HPMC to skin in a dermal irritancy study (<sup>3</sup>CTFA, 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 response.

### ***Analogues***

The acute dermal toxicity of ethyl cellulose was evaluated in rabbits (sex and strain not reported) (<sup>47</sup>Moreno, 1977). The LD<sub>50</sub> was reported to be greater than 5000 mg/kg/day. Dermal irritancy of hydroxypropyl cellulose has also been evaluated in human subjects (<sup>14</sup>CTFA, 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.

## **Repeated Dose Toxicity**

### ***HPMC***

Numerous short-term and subchronic toxicity studies of HPMC in several species of test animals have been undertaken.

In the most recent subchronic toxicity study, low-viscosity HPMC (2.83 cps, USP 2910) was administered to Crj:CD (SD) rats by oral gavage for three months at doses of 505, 1020, and 2100 mg/kg/day (<sup>53</sup>Obara *et al.*, 1999). The only finding

attributed to treatment, decreased body weight, was in rats at the high dose only. Sporadic findings in hematology, blood chemistry, organ weights, and pathology were considered unrelated to treatment.

<sup>8</sup>Wyatt *et al.* (1988) fed Wistar rats 0 or 100g HPMC / kg for 12 days. HPMC was considered to cause an enlargement of the cecum and colon associated with increased contents and organ weights. The density of bacteria in the cecum was reduced compared to fiber-free controls. The authors considered the increased cecum and colon size to be related to increased content bulk.

<sup>2</sup>Hodge *et al.* (1950) conducted a 30-day dietary toxicity study containing 0, 2, 10 or 25% HPMC (USP 1828) in the diets of 10 male and 10 female rats (strain not reported) per group (25% in the diet is approximately 13,500 mg/kg/day for a 250g rat). Diarrhea and a decrease in body weight gain were noted in the high dose group. There were no histological findings noted, nor were any abnormalities found in the blood or urine.

<sup>5</sup>McCollister *et al.* (1961) evaluated the potential toxicity of HPMC (USP 1828 and 2208) in male and female rats of Wistar lineage at dose levels of 0, 0.3, 1, 10, and 20% in the diet for 84 and 90-days. At 20% in the diet, there was up to 30% mortality and a marked retardation in body weight gain of treated rats. At 10% in the diet, males displayed a smaller decrease in body weight gain. There were no other in-life observations in any dose group. There were no findings upon gross or histopathological examination.

The effects of differing viscosity of HPMC upon potential toxicity were evaluated in two 90-day studies in rats. <sup>6</sup>McCollister & Copeland (1967), <sup>7</sup>McCollister *et al.* (1973), and <sup>7a</sup>Mitchell (1967) fed four groups of male and female rats (strain not reported) 0, 1, 3 or 10% HPMC of varying viscosities in the diets. The viscosities of the HPMC evaluated were 10, 4000, 8480, 31,800, and 50,000 cps representing substitution types USP 1828, 2906, and 2910. No adverse effects upon mortality, growth, general appearance and behavior, body weights, food consumption, hematological and serum chemistry analysis, organ weights, and gross and histopathologic changes were noted up to 31,800 cps. Rats fed 50,000 cps up to 20% in the diet were noted with intestinal dilation at necropsy, decreases in globulins, and increased specific gravity and lower pH of the urine secondary to dehydration from loose stools associated with the test material administration.

<sup>9</sup>Schwetz *et al.* (1973) also found no adverse effects of low viscosity (4.22cP) HPMC (USP 2910) when fed to Sprague-Dawley rats at 0, 1, and 5% in their diets for 90-91 days. Parameters evaluated included; body weight, food consumption, mortality, urine and hematology parameters, serum chemistry, organ weights, and gross and histopathological evaluation of tissues.

<sup>4</sup>McCollister & Oyen (1954) fed male and female rats of Wistar lineage diets containing 0, 1, 3, 10 or 30% HPMC (a material with a substitution range between

that of USP 2906 and 2910) for 121 days. They reported 50% mortality and severe decreased body weight gains in groups of rats ingesting the 30% HPMC diet. Male body weight gain was also decreased in the 10% group; however, no other treatment related effects were noted in in-life parameters or gross and histopathological examinations at any dose level.

<sup>2</sup>Hodge *et al.* (1950) reported no adverse findings in rabbits (sex and strain not reported) ingesting diets containing 1, 10 or 25% HPMC for 30 days.

Toxicity studies of HPMC of widely varying viscosities conducted in dogs have also failed to identify any significant treatment related effects. <sup>2</sup>Hodge *et al.* (1950) administered an HPMC “having a higher gel point by 10-15 °C than regular Methocel™” to dogs (sex and strain not specified) at up to 25% in the diet for 30 days resulting in diarrhea and minor decreases in body weights. Administration of up to 3000 mg/kg/day of the same test material to dogs for a year produced no observable effects following a relatively comprehensive evaluation, including histopathology. <sup>9a</sup>Mitchell (1967) provided male and female Beagle dogs with up to 9.6% HPMC (50,000 cps) 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. <sup>7</sup>McCollister *et al.* (1973), and <sup>9</sup>Schwetz *et al.* (1973) found no effects on male and female Beagle dogs ingesting diets containing up to 5% and 6% of lower viscosity HPMCs (4.22 cps and 10 cps, respectively).

### **Analogues**

The toxicity of hydroxypropyl cellulose has also been evaluated. Ingestion by rats (sex and strain not reported) of up to approximately 5000 mg/kg/day via the diet for 90 days resulted in no untoward effects (<sup>12</sup>IBL, 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 hemoglobin level in rats (sex and strain not available) fed 6000 mg/kg/day (<sup>16</sup>Kitagawa *et al.*, 1978b).

Ethylhydroxyethyl cellulose was evaluated in a 90-day dietary toxicity study in male and female CD rats (<sup>18</sup>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/day; however, this was not accompanied by histopathological changes in liver tissues.

The toxicity of methyl cellulose to rats has been evaluated in several subchronic toxicity studies employing a variety of dosing regimen. No adverse effects have been reported in male and female rats (strain not reported) ingesting diets containing up to 50% methyl cellulose for 90-days or up to 5% for 6 and 8 months (<sup>24</sup>Bauer *et al.*, 1944; <sup>25</sup>Bauer and Lehman, 1951). No adverse effects were reported in male and female albino rats provided drinking water containing up to

1% methyl cellulose for 8 months (<sup>23</sup>Deichmann and Witherup, 1943). Administration of methylcellulose to rats (sex and strain not reported) as 1-2.5% solutions via intravenous or interperitoneal injection for 10-112-days resulted in increased spleen weight, arterial hypertrophy, and methyl cellulose deposits in renal glomeruli (<sup>26</sup>Ellingson and Massengale, 1952; <sup>27</sup>Hall and Hall, 1962; <sup>28</sup>Fitch *et al.*, 1962; <sup>29</sup>Lawson and Smith, 1968). Finally, providing two dogs (sex and strain not reported) up to 100 grams methyl cellulose for four weeks reportedly caused no adverse effects (<sup>30</sup>Bauer, 1975).

## Genetic Toxicity

### *HPMC*

HPMC has been directly evaluated in a Rat Bone Marrow Cytogenetics (chromosomal aberrations) conducted using rats ingesting a 5% diet of HPMC (USP 2910) for 90 days (<sup>9b</sup>Johnson *et al.*, 1977). Extensive evaluations of analogues of HPMC have been undertaken and found to be negative.

### *Analogues*

Methyl cellulose has been extensively tested, and has produced negative results in two Ames' bacterial mutagenicity studies (<sup>31</sup>Blevins and Taylor, 1982; <sup>32</sup>Ishidate *et al.*, 1984), a bacterial reverse mutagenesis study (<sup>33</sup>Litton Bionetics, 1974), a mitotic recombination study (<sup>32</sup>Ishidate *et al.*, 1984), two chromosomal aberration induction assays (<sup>32</sup>Ishidate *et al.*, 1984), and a dominant lethal assay (<sup>32</sup>Ishidate *et al.*, 1984).

## Carcinogenicity

### *HPMC*

<sup>2</sup>Hodge *et al.* (1950) evaluated HPMC (USP 1828) in a two-year dietary study conducted in male and female rats (strain not reported). Groups of male and female rats were fed diets containing 0, 1, 5 or 20% HPMC. The only treatment related effect observed was a slight retardation of body weight gain in males at the highest dose level. No treatment-related increase in the incidence of tumors was reported indicating a lack of carcinogenic potential of HPMC.

### *Analogues*

Methylethyl cellulose and methyl cellulose have been evaluated in chronic toxicity and oncogenicity studies. Male and female rats (strain not reported) were provided diets containing up to 1% methylethyl cellulose (<sup>45</sup>ICI, 1961), or up to 5% methyl cellulose in male and female Sprague Dawley rats (<sup>7</sup>McCollister *et al.*, 1973) for two years in two separate bioassays. Neither compound demonstrated oncogenic potential.

## Reproductive & Developmental Toxicity

### *HPMC*

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 subchronic duration or longer. No specific developmental toxicity studies of HPMC have been conducted; however, the relative lack of absorption of HPMC and subsequent systemic exposure (see below), and the lack of developmental toxicity of close analogues, indicate a lack of potential HPMC developmental toxicity. This conclusion is consistent with that of the Select Committee on GRAS Substances who concluded, "There is no evidence in the available information on hydroxypropylmethyl 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 (21 CFR 121.1021)" (FASEB, 1974).

### **Analogues**

Hydroxypropyl cellulose ("low substitution") had no adverse effects on the reproductive abilities of the F1 offspring from a teratology study in Wistar rats at dose levels up to 5000 mg/kg bw/day in rats (<sup>15</sup>Kitagawa *et al.*, 1978<sub>a</sub>). Mean litter weights and pre-implantation loss were increased at the 5000 mg/kg bw/day in the teratology phase of the study, however, at a dose level of 1,000 mg/kg bw/day there were no adverse effects. In no case was there a teratogenic effect. Hydroxypropyl cellulose ("low substitution") did not cause teratogenic effects in Himalayan rabbits at levels up to 5000 mg/kg bw/day (<sup>16</sup>Kitagawa *et al.*, 1978<sub>b</sub>). Except for an increased preimplantation loss at 5,000 mg/kg bw/day, the sporadic adverse effects noted in the various litters were not dose related. At levels of 1,000 mg/kg bw/day there were no adverse effects on implantation. Methyl cellulose has been evaluated for developmental toxicity in female mice, rats, and rabbits (strains not reported) in several studies (<sup>35</sup>Cannon Labs, 1975; <sup>36</sup>1977; <sup>34</sup>FDRL, 1973). The only observation noted was a delay in ossification of the ribs in rat fetuses. There was also a reduced pregnancy rate noted in females fed 1600 mg/kg/day, and an increase in resorption rates, but methyl cellulose was not considered to be a reproductive toxin.

## **Pharmacokinetics & Metabolism**

### **HPMC**

The pharmacokinetics and potential metabolism of HPMC have been evaluated in rats and humans using <sup>14</sup>C-HPMC labeled in the methoxyl position by methyl capping of the hydroxypropyl groups. In male and female Sprague-Dawley rats administered 500mg of <sup>14</sup>C-HPMC as single or repeated bolus doses, greater than 98% of administered <sup>14</sup>C was excreted via the feces in the absence of any appreciable biliary excretion (<sup>10</sup>Gorzinski *et al.*, 1986). Approximately 1% was found to be excreted via the urine; however, subsequent experiments demonstrated that much of this was from fecal contamination of urine samples and that a more accurate value was approximately half this much. Only approximately 0.2% of administered <sup>14</sup>C was found in the carcass and tissues and this was present primarily in the intestinal tract. Trace amounts of radioactivity

observed in blood had an excretory half-life from plasma of approximately 2 hours. Analysis of urinary <sup>14</sup>C revealed mono-, di- and tri- glucose molecules approximately equivalent to that found as impurities in the test HPMC used. These data demonstrated a general lack of absorption upon ingestion, lack of systemic exposure, and lack of potential accumulation in tissues.

In another study, cecal contents of 2 male Wistar rats were incubated *in vitro* in a complex medium broth with 2 mg/mL of HPMC (<sup>8</sup>Wyatt *et al.*, 1988). HPMC was resistant to metabolism with a maximum of 5% degradation in 48 hours and nothing further through 7 days. There was no visible degradation of the cellulose fibers or changes in viable bacterial counts compared to the control incubations.

### **Analogues**

A similar disposition of <sup>14</sup>C-hydroxyethyl cellulose as noted for HPMC was demonstrated in male and female CDF rats (<sup>50</sup>Sullivan *et al.*, 1968a) and in male and female CDF rats and dogs (sex and strain not reported) (<sup>51</sup>Sullivan *et al.*, 1968b). Methyl cellulose has also been reported to be excreted nearly exclusively via the feces within 48 hours (<sup>37</sup>Braun *et al.*, 1974). Methylethyl cellulose was also recovered 90% in the feces within 96 hours following a single 0.6g/kg bolus dose.

## **Human Data**

### **HPMC**

Metabolism and laxative effects data for HPMC have been collected in human subjects. Twenty-five adults (sex not reported) ingested HPMC (USP 1828) in doses ranging from 0.6-8.9g on three separate occasions (<sup>11</sup>Knight *et al.*, 1952). Only a mild laxative or constipating effect was noted in several cases. Approximately 97% of the dose, determined as methoxy groups, was recovered from feces.

### **Analogues**

Human data has also been collected for ethylhydroxyethyl cellulose and methyl cellulose. Ethylhydroxyethyl cellulose was administered in doses of 1.0-1.5g, three times daily, for at least 2 months to 85 male and female ambulatory patients (aged 21-75 years) with intestinal problems (<sup>19</sup>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. Data for methylcellulose was gathered in several studies of more than 100 persons given as much as 6g of methylcellulose daily for up to 23 days (<sup>22</sup>Tainter, 1943, 3 persons; <sup>30</sup>Bauer, 1975, unspecified number; <sup>39</sup>Schweig, 1948, 37 persons; <sup>40</sup>Bargen, 1949, unspecified number; <sup>41</sup>Crane *et al.*, 1969, two persons; <sup>42</sup>Eastwood *et al.*, 1988, five males; <sup>43</sup>Hamilton *et al.*, 1988, 50 persons). Transient changes in fecal consistency and movement frequency were

consistently noted. Other observations included: sodium and water retention, increased serum osmolality, reduced urinary aldosterone excretion, and small reductions in fecal volatile fatty acids and neutral sterols.

c. Toxicology Table

Summary Toxicity Data for HPMC GRAS Submission

	Hydroxypropyl-methyl Cellulose	Hydroxypropyl Cellulose	Ethyl Hydroxyethyl Cellulose	Methyl Cellulose	Methyl Ethyl Cellulose	Ethyl Cellulose
Acute Oral Toxicity	<sup>1</sup> LD <sub>50</sub> in rats > 1000 mg/kg/day <sup>2</sup> LD <sub>50</sub> in rats > 4000 mg/kg/day	<sup>12,13</sup> LD <sub>50</sub> in rats = 10,200-15,000 mg/kg/day	<sup>17</sup> LD <sub>50</sub> in rats = 5000-10000 mg/kg/day	<sup>20</sup> In man, single oral doses of 5g and 10g were well tolerated.		<sup>48</sup> LD <sub>50</sub> in rats = 5000 mg/kg/day
Acute Dermal Toxicity						<sup>48</sup> LD <sub>50</sub> in rabbits > 5000 mg/kg/day
Acute Toxicity- Other Routes	<sup>2</sup> LD <sub>50</sub> IP in rats = 5000 mg/kg/day  <sup>2</sup> LD <sub>50</sub> IP in mice = 5000 mg/kg/day			<sup>21</sup> In dogs, single IV injection of 40 mL of 0.7-2.8% solutions in saline - anemia, leucopenia and increased sedimentation rate.		
Dermal Irritation	<sup>3</sup> Repeated Rabbit dermal irritation study (10 applications)	<sup>14</sup> Repeated human patch testing (50 subjects, 10	<sup>17</sup> In abraded skin of albino rabbits, very mild irritant			

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	of 24 h each), intact and abraded skin, dry or moistened (dose not given). Minor erythema secondary to skin adhesion of moistened and no systemic effects.	repeated patches of 10% aqueous solution plus rechallenge) resulted in no irritation.	reactions (0.75-1.0).			
Dermal Sensitization		<sup>14</sup> Repeated human patch testing (50 subjects, 10 repeated patches of 10% aqueous solution plus rechallenge) resulted in no sensitization.	<sup>17</sup> Negative in the guinea pig by Kligman's maximization test.			
Repeated-Dose Toxicity	<sup>53</sup> Rats given HPMC by oral gavage for 3 months = decreased body weight in high dose animals  <sup>4-8</sup> Up to 121-day	<sup>12</sup> 90-day dietary study in rats = increased food consumption at high dose only (~5000 mg/kg/day)  <sup>13</sup> 6-month	<sup>18</sup> 90-day dietary study in rats = decrease in liver relative weights, no histopathologic correlate @ 2500 mg/kg/day	<sup>23</sup> 95-day dietary study in rats up to 10% in diet = no significant findings.  <sup>23</sup> 8-month drinking water	<sup>44</sup> Data from short-term tests indicate that 3g daily in the diet had no effect in rats.	<sup>48</sup> NOEL > 182 mg/kg/day

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	<p>dietary studies in rats: up to 30% in diet. Mortality and decreased bodyweight noted at 25% and 30% doses but only decreased body weight at 20% or lower doses. No histopathological changes noted.</p> <p><sup>2</sup>Up to 25% in diets of rabbits for 30 days, no findings noted.</p> <p><sup>7,9,9a</sup>Up to 9.6% in diet of dogs for up to 94 days. Only decreased body weight at 9.6% but, no significant findings noted at 6% or lower.</p>	<p>dietary study in rats = decreased hemoglobin at 6000 mg/kg/day</p>	<p>(highest dose tested).</p>	<p>study in rats up to 1% in water = no significant findings.</p> <p><sup>24,25</sup>6&amp;8-month dietary studies in rats up to 5% in diets = no significant findings.</p> <p><sup>25</sup>90-day diet study in rats up to 50% in diet = no significant findings.</p> <p><sup>26-29</sup>10-112 day IP/IV studies in rats (1-2.5% solutions) = increased spleen weight, MC deposits in renal glomeruli, arterial hypertension.</p> <p><sup>30</sup>4-week dog dietary study</p>		
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				up to 100g daily = no significant findings.		
Genetic Toxicity	<sup>9b</sup> Negative cytogenetics (chromosome aberration) assay of bone marrow cells from rats administered up to 5% HPMC for 90 days.			Negative in <sup>31,32</sup> AMES, <sup>33</sup> reverse mutagenesis, <sup>33</sup> mitotic recombination, <sup>32</sup> chromosomal aberration, <sup>33</sup> C.A. induction, <sup>33</sup> dominant lethal assays.		
Carcinogenicity	<sup>2</sup> Up to 20% in diet of rats, negative for carcinogenicity			<sup>7</sup> 2-year dietary study in SD rats up to 5% in diet = negative	<sup>45</sup> 2-year dietary study in rats and mice up to 1% in diet = negative  <sup>44</sup> 2-year dietary study in mice and rats = body weight reduced in males at high dose (1% in diet). No other observations	

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					noted in-life or at necropsy.	
Reproductive Toxicity	<sup>5,6,7,9</sup> Lack of gonadal toxicity in several subchronic repeated dose studies in males and females of several species.	<sup>15</sup> At 5000 mg/kg/day in rats, no effect on progeny reproduction.		<sup>34</sup> Reduced pregnancy rate in surviving high-dose females (1600 mg/kg/day), increase in resorption rates.		
Developmental Toxicity		<sup>15,16</sup> Non-teratogenic at 5000 mg/kg bw/day in rats and rabbits. Preimplantation loss at 5000 mg/kg bw/day, absent at 1000 mg/kg bw/day.		<sup>35</sup> Non-teratogenic in mice.  <sup>34,36</sup> Non-teratogenic in rats; increased centers of ossification in ribs of rat fetuses.  <sup>34</sup> Non-teratogenic in rabbits.		
Pharmacokinetics & Metabolism	<sup>10</sup> >99% excreted in feces after a single bolus dose. After 5 repeated doses,	<sup>12,13</sup> 98.32% - 102.7% of ingested material is excreted in the		<sup>37</sup> 102.2% of a bolus dose of 500 mg/kg was excreted via feces within 48	<sup>46</sup> 90% of a single 0.6g dose recovered in feces by 96 hours.	

	97-102% was excreted via feces suggesting no tendency of accumulation in tissues.	feces in the first 48-96 hours.		hours. <sup>38</sup> Some evidence of transference to pups via milk, causing transient anemia in pups.		
Human Data	<sup>11</sup> 97% of the dose (3x up to 8.9g) was recovered in feces. Only mild laxative or constipating effect noted.		<sup>19</sup> Given 1.0-1.5g 3x daily for >2 months to humans with GI problems. No toxicity noted.	<sup>22,30,39-43</sup> Up to 6g as long as 23 days orally: transient changes in fecal consistency & movement frequency.		

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#### **d. Possible Residuals**

Based on the reaction chemistry there is the potential for residual impurities that could include propylene oxide (residual reactant) and propylene chlorohydrin isomers. Therefore, eleven different lots of HPMC from three different production sites were submitted for the quantitative analysis of propylene oxide and two propylene chlorohydrin isomers by mass spectrometry. Two separate extraction and analysis methods were employed to quantitatively determine these components in the HPMC samples. Accurately weighed portions of the submitted HPMC samples were solvent extracted and aliquots of these extracts were analyzed by multiple ion detection (MID) gas chromatography mass spectrometry (GC/MS) operating in the electron impact (EI) ionization mode. Authentic standard solutions of known concentrations of the two propylene chlorohydrin isomers, i.e. 1-chloro-2-propanol (1C2P) and 2-chloro-1-propanol (2C1P), along with the internal standard, 3-chloro-1-propanol (3C1P), were used to quantitatively determine 1C2P and 2C1P concentrations in the eleven HPMC samples in the first method. Additionally, authentic standard solutions of propylene oxide (PO) along with the internal standard, methylene chloride, were also used to quantitatively determine PO concentrations in the eleven HPMC samples in the second method.

No detectable amount of 1C2P or 2C1P was present in any of the eleven HPMC samples analyzed. The detection limits were 16.9 µg/kg and 37.5 µg/kg for 1C2P and 2C1P, respectively. The recovery of 1C2P and 2C1P from the one fortified HPMC sample was 90.5% and 50.9%, respectively.

No detectable amount of propylene oxide (PO) was present in any of the eleven HPMC samples analyzed. The detection limit of PO was calculated to be 21 µg/kg of HPMC. The recoveries of PO in the two fortified HPMC samples were 55.0% and 49.5% at concentrations of 101 µg/kg and 201 µg/kg in the HPMC samples, respectively.<sup>52</sup> FDA's VSD (virtually safe dose) for exposures to propylene oxide as a dietary contaminant is 1.4 µg per person per day.<sup>54</sup> The oral daily dose of PO can be calculated to be 0.42 µg /day (20 grams per day HPMC x 0.021 µg/g (limit of detection for PO)) which gives a Margin of Safety of 3.3 when using FDA's VSD and the detection limit for PO as the residual concentration.

The presence of these residuals is not expected and the analysis for these residuals was performed as an additional demonstration of safety. Dow expects no other residuals to be present based on the product's chemistry and the manufacturing process.

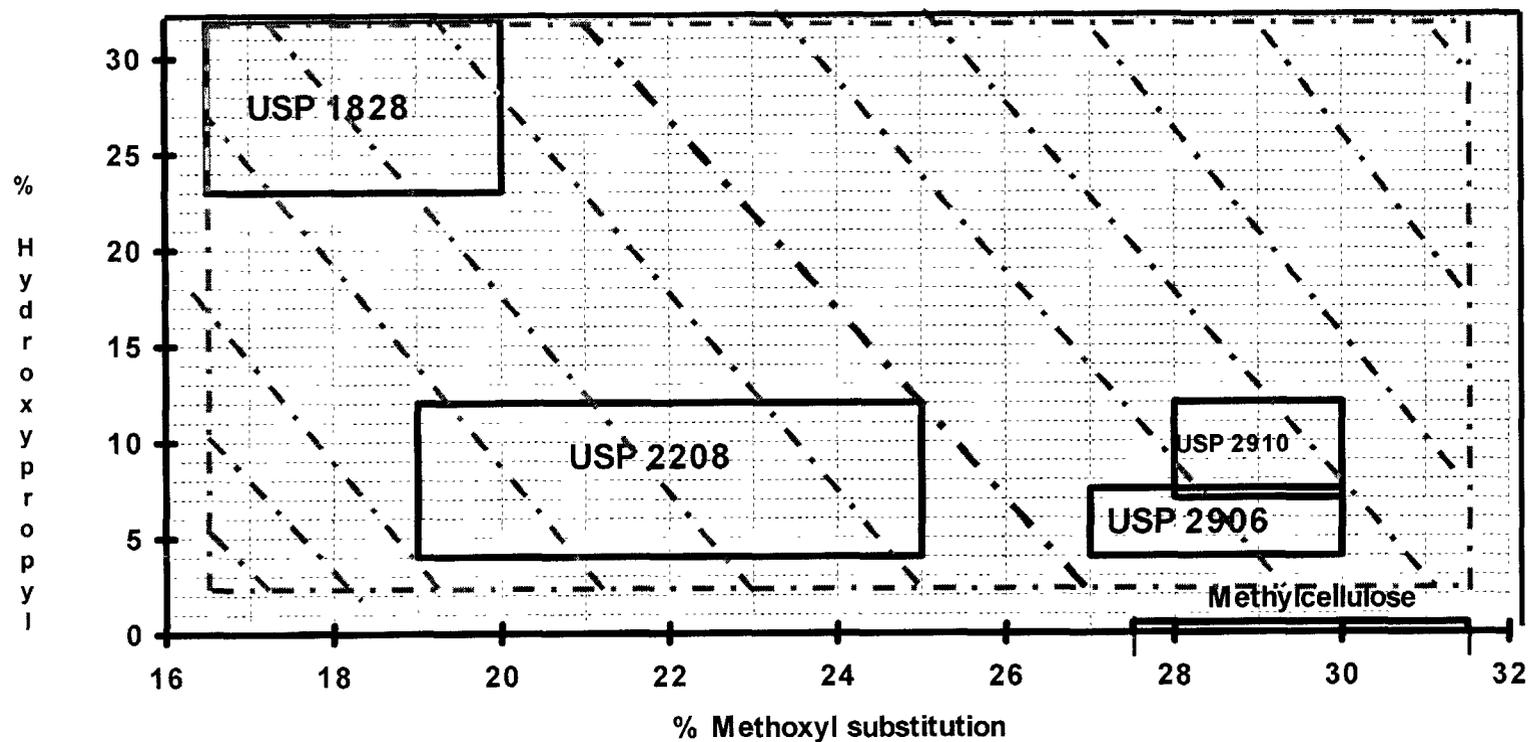
#### **IV. Conclusions**

Based on the documentation provided in this GRAS notification, and as discussed above, Dow Chemical Company has concluded that HPMC is GRAS via scientific procedures for use in food for multiple technical effects and as a dietary fiber, at levels up to 20 grams/day.

Appendix

**Appendix A**

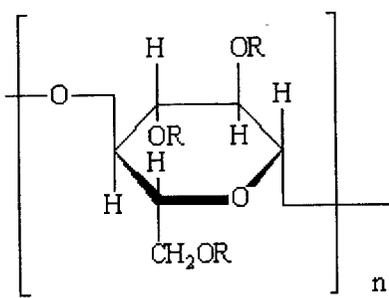
Current and Proposed % Substitution Limits for Hydroxypropyl Methylcellulose for Food Uses



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## HYDROXYPROPYLMETHYL CELLULOSE

Prepared at the 29th JECFA (1985), published in FNP 34 (1986) and in FNP 52 (1992)

SYNONYMS	INS No. 464
DEFINITION	A methyl cellulose modified with a small amount of 2-hydroxypropyl groups attached through ether links to anhydroglucose units of the cellulose. The article of commerce may be further specified by viscosity.
CHEMICAL NAMES	Hydroxypropyl methylcellulose, 2-hydroxypropyl ether of methyl cellulose
C.A.S. NUMBER	9004-65-3
CHEMICAL FORMULA	$[C_6H_7O_2(OH)_x(OCH_3)_y(OCH_2CHOHCH_3)_z]_n$ where $z = 0.07 - 0.34$ $y = 1.12 - 2.03$ $x = 3 - (z + y)$ : ( $z + y =$ degree of substitution)
STRUCTURAL FORMULA	 <p>where R = H or CH<sub>3</sub> or CH<sub>2</sub>CHOHCH<sub>3</sub></p>
FORMULA WEIGHT	Unsubstituted structural unit: 162.14. Structural unit with 1.19 degree of substitution: approx. 180. Structural unit with 2.37 degree of substitution: approx. 210. Macromolecules: from about 13,000 (n about 70) up to about 200,000 (n about 1000)
ASSAY	Not less than 19% and not more than 30% of methoxyl groups (-OCH <sub>3</sub> ) and not less than 3% and not more than 12% hydroxypropoxyl groups (-OCH <sub>2</sub> CHOHCH <sub>3</sub> ), on the dried basis

DESCRIPTION Hygroscopic white or off-white powder, or granules or fine fibres

FUNCTIONAL USES Emulsifier, thickening agent, stabilizer

## CHARACTERISTICS

### IDENTIFICATION

*Solubility* Swelling in water, producing a clear to opalescent, viscous colloidal solution; insoluble in ethanol

*Foam formation* A 0.1% solution of the sample is shaken vigorously. A layer of foam appears. This test permits the distinction of sodium carboxymethyl cellulose from other cellulose ethers.

*Precipitate formation* To 5 ml of a 0.5% solution of the sample, add 5 ml of a 5% solution of copper sulfate or of aluminium sulfate. No precipitate appears. This test permits the distinction of sodium carboxymethyl cellulose from other cellulose ethers.

*Substituents* Determine the substituents by gas chromatography

*Loss on drying* Not more than 10% (105° C to constant weight)

*pH* Not less than 5 and not more than 8 (1 in 100 soln)

*Sulfated ash* Not more than 1.5% for products with viscosities of 50 centipoises or above, and not more than 3% for products with viscosities below 50 centipoises Test 1 g of the sample (Method I)

*Propylene chlorohydrins* Not more than 0.1 mg/kg  
See description under TESTS

*Arsenic* Not more than 3 mg/kg (Method II)

*Lead* Not more than 10 mg/kg

*Heavy metals* Not more than 40 mg/kg  
Test 0.5 g of the sample as directed in the Limit Test (Method II)

## PURITY TESTS

Propylene  
chlorohydrins

### Apparatus

Instrument: Varian 3700 gas chromatograph.

Column:

- material: glass
- length: 4 m
- internal diameter: 2 mm
- liquid phase: 100% SP1000 (Supelco)

Temperatures:

- injector: 220o
- column: 55o programmed to 180o at 5o/min
- detector: 250o

Carrier gas: nitrogen

Flow: 30 ml/min.

Volume injected: 1 µl

Detector: FID

### Reagents

- Diethyl ether
- 1-Chloro-2-propanol, 97%
- Mixture of 1-chloro-2-propanol (75% w/w) and 2-chloro-1-propanol (24% w/w)
- 3-Chloro-1-propanol
- Diethyl ether, containing 12.5 µg 3-chloro-1-propanol per ml
- Standard solution in ether, prepared from the "mixture of 1-chloro-2-propanol (75% w/w) and 2-chloro-1-propanol (24% w/w)" and "3-Chloro-1-propanol" containing:
  - 1-chloro-2-propanol: 8.5 µg/ml
  - 2-chloro-1-propanol: 2.7 µg/ml
  - 3-chloro-1-propanol (internal standard): 12.5 µg/ml.

### Procedure

Weigh 1 g sample, add 5.0 ml ether with internal standard (e.) and shake the mixture for 2 h. After sedimentation (centrifuging may be necessary) 2-3 µl of the clear supernatant is injected into the gas chromatograph.

Measure peak heights of GC peaks. Retention times are approximately 14.2 and 15.8 min for 1-chloro-2-propanol and 2-chloro-1-propanol respectively.

Internal standard 3-chloro-1-propanol is at 20.6 min. When interferences are observed, mass spectroscopy may be used to verify.

### Calculation

Calculate the amount of 1-chloro-2-propanol (1-CP) in the sample with the formula:

$$\text{Amount (mg/kg)} = \frac{(H: 1-CP)_{\text{sample}}}{(H: \text{intern. stand.})_{\text{sample}}} \times \frac{(H: \text{intern. stand.})_{\text{stand. soln}}}{(H: 1-CP)_{\text{stand. soln}}} \times \frac{8.5 \times 6.0}{W}$$

where

H = peak height of 1-CP or the internal standard

W = sample weight in grams

For 2-chloro-1-propanol a similar formula is used, with a factor 2.7 instead of 8.5 (see composition of standard solution in ether under "Reagents")

### Detection limit

The detection limit is circa 0.04 mg/kg for 1-chloro- 2-propanol and circa 0.08 mg/kg for 2-chloro-1-propanol.

### Blanks

Blank determinations carried out, only using the reagents, give no measurable signals.

## METHOD OF ASSAY

### Determination of the hydroxypropoxyl group

#### Apparatus

The apparatus for hydroxypropoxyl group determination is shown in the accompanying diagram. The boiling flask, D, is fitted with an aluminium foil-covered Vigreux column, E, on the sidearm and with a bleeder tube through the neck and to the bottom of the flask for the introduction of steam and nitrogen. A steam generator, B, is attached to the bleeder tube through Tube C, and a condenser, F, is attached to the Vigreux column. The boiling flask and steam generator are immersed in an oil bath, A, equipped with a thermo-regulator such that a temperature of 155°C and the desired heating rate may be maintained. The distillate is collected in a 150-ml beaker, G, or other suitable container.

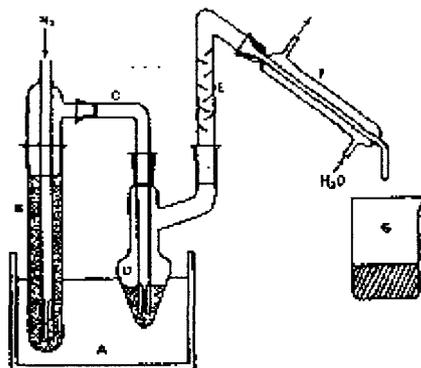


Figure Apparatus for Hydroxypropyl Determination

### Procedure

Transfer about 100 mg of the sample, previously dried at 105° for 2 h and accurately weighed, into the boiling flask, and add 10 ml of chromium trioxide solution (60 g in 140 ml of water). Immerse the steam generator and the boiling flask in the oil bath (at room temperature) to the level of the top of the chromium trioxide solution. Start cooling water through the condenser and pass nitrogen gas through the boiling flask at the rate of one bubble per sec. Starting at room temperature, raise the temperature of the oil bath to 155° over a period of not less than 30 min, and maintain this temperature until the end of the determination. Distil until 50 ml of the distillate is collected. Detach the condenser from the Vigreux column, and wash it with water, collecting the washings in the distillate container. Titrate the combined washings and distillate with 0.02 N sodium hydroxide to a pH of 7.0, using a pH meter set at the expanded scale.

NOTE: Phenolphthalein TS may be used for this titration, if it is also used for all standards and blanks.

Record the volume,  $V_a$  of the 0.02 N sodium hydroxide used. Add 500 mg of sodium bicarbonate and 10 ml of dilute sulfuric acid TS, and then after evolution of carbon dioxide has ceased, add 1 g of potassium iodide. Stopper the flask, shake the mixture, and allow it to stand in the dark for 5 min. Titrate the liberated iodine with 0.02 N sodium thiosulfate to the sharp disappearance of the yellow colour, confirming the end-point by the addition of a few drops of starch TS. Record the volume of 0.02 N sodium thiosulfate required as  $Y_a$ .

Make several reagent blank determinations, using only the chromium trioxide solution in the above procedure. The ratio of the sodium hydroxide titration (Vb) to the sodium thiosulfate titration (Yb), corrected for variation in normalities, will give the acidity-to-oxidizing ratio,  $V_b/Y_b = K$ , for the chromium trioxide carried over in the distillation. The factor K should be constant for all determinations.

Make a series of blank determinations using 100 mg of methyl-cellulose (containing no foreign material) in place of the sample, recording the average volume of 0.02 N sodium hydroxide required as  $V_m$  and the average volume of 0.02 N sodium thiosulfate required as  $Y_m$ .

Calculate the hydroxypropoxyl content of the sample, in mg, by the formula:

$$75.0 \times [N_1 (V_a - V_m) - k N_2 (Y_a - Y_m)]$$

where

$N_1$  = the exact normality of the 0.02 N sodium hydroxide solution

$N_2$  = the exact normality of the 0.02 N sodium thiosulfate solution

$$k = V_b N_1 / Y_b N_2$$

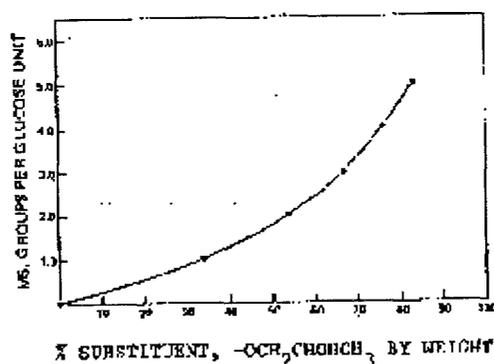


Chart for converting percentage of substitution, by weight, of hydroxypropoxyl groups to molecular substitution per glucose unit.

### Determination of the methoxyl group

See Apparatus and Procedure in Ethoxyl and Methoxyl Group Determination and determine the content of methoxyl group (-OCH<sub>3</sub>).

**Calculation**

Calculate as percentage. Correct the % of methoxyl groups thus determined by the formula:

$$A - (B \times 0.93 \times 31 / 75)$$

where

A = the total % of -OCH<sub>3</sub> groups determined

B = the % of -OCH<sub>2</sub>CHOHCH<sub>3</sub> determined in the Method of Assay for Hydroxypropoxyl group content

0.93 = an average obtained by determining, on a large number of samples, the propylene produced from the reaction of hydriodic acid with hydroxypropoxyl groups during the Method of Assay for methoxyl groups (-OCH<sub>3</sub>).

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Pages 000044 - 000047 have been removed in accordance with copyright laws. Please see appended bibliography list of the references that have been removed from this request.



necessary, wash down the solution in the bottle with a small quantity of water. Add 1 drop of methyl orange TS, and after neutralizing with ammonia TS, ammonia solution (28) or dilute hydrochloric acid, add 5 mL of diluted hydrochloric acid (1 in 2) and 5 mL of potassium iodide TS, and allow to stand for 2 to 3 minutes. Add 5 mL of acidic tin (II) chloride TS, and allow to stand for 10 minutes. Then add water to make 40 mL, add 2 g of zinc for arsenic analysis, and immediately connect the rubber stopper H fitted with B and C with the generator bottle A. Transfer 5 mL of the absorbing solution for hydrogen arsenide to the absorber tube D, insert the tip of C to the bottom of the absorber tube D, then immerse the generator bottle A up to the shoulder in water maintained at 25°C, and allow to stand for 1 hour. Disconnect the absorber tube, add pyridine to make 5 mL, if necessary, and observe the color of the absorbing solution: the color produced is not more intense than the standard color.

Preparation of standard color: Measure accurately 2 mL of Standard Arsenic Solution in the generator bottle A. Add 5 mL of diluted hydrochloric acid (1 in 2) and 5 mL of potassium iodide TS, and allow to stand for 2 to 3 minutes. Add 5 mL of acidic tin (II) chloride TS, allow to stand at room temperature for 10 minutes, and then proceed as directed above. The color produced corresponds to 2  $\mu$ g of arsenic (III) trioxide ( $As_2O_3$ ) and is used as the standard.

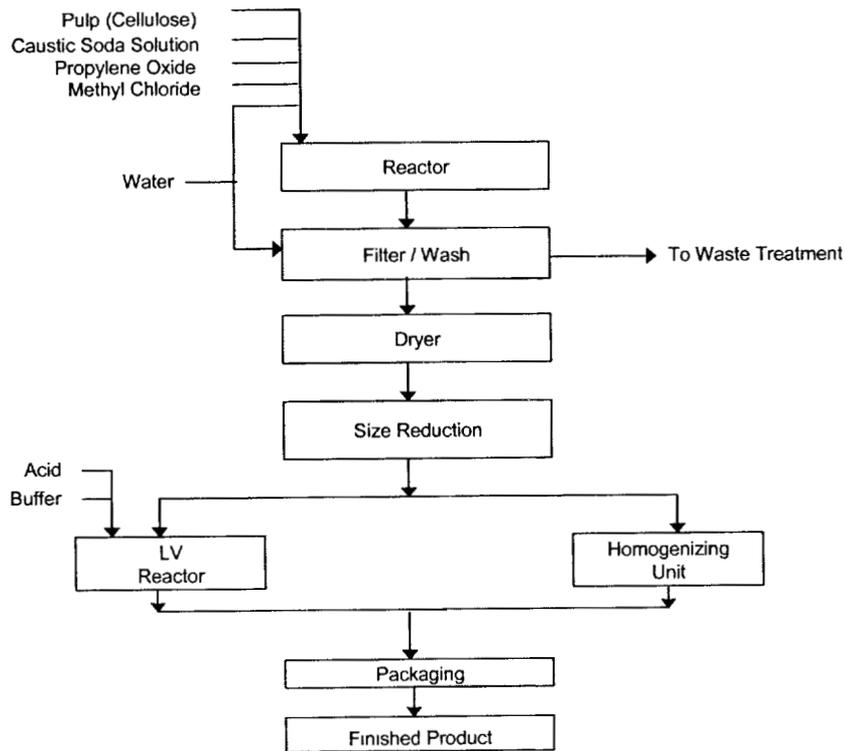
Note: Apparatus, reagents and test solutions used in the test should contain little or no arsenic. If necessary, perform a blank determination.

Pages 000050 - 000051 have been removed in accordance with copyright laws. Please see appended bibliography list of the references that have been removed from this request.

## **Appendix B**

## Appendix B: Process Flow Diagram

### *METHOCEL\* Cellulose Ethers Process Flow Diagram*



## Appendix C

## **BUILDINGS AND FACILITIES**

The described operations are conducted in buildings and facilities within the manufacturing complex of Dow in various locations globally. The buildings, laboratories and process areas are designed for proper operation and are maintained in a clean and orderly manner. An adequate supply of potable water, restrooms and ventilation is provided.

The HPMC process functions with computer-assisted control to allow for continuous monitoring of process variables and to maximize product consistency. All products are made by utilizing a recipe (Master Production Record). The recipe values include variables such as temperature, pressure, weights, flow rates, and raw material selections. The computer control allows for monitoring throughout the process to yield a characterization of the process during a product campaign. The data is continuously recorded and both manually and automatically analyzed for continuous improvement and to flag any deviations in the process. The computer control allows for improved consistency both plant-to-plant and within a plant from product-to-product.

## **EQUIPMENT**

All processing equipment, raw material storage vessels, and packaging equipment are constructed of materials which are non-reactive, non-additive and non-absorptive to the extent that might alter the safety, identity, quality or purity of the finished products. As required, the equipment is cleaned according to written procedures and is maintained in good operating condition.

## **HPMC MANUFACTURING PROCESS**

### **A. PRODUCTION**

This next section breaks down the production of HPMC into sections and explains both the equipment and process in each section. See Appendix B for a process flow diagram.

#### **1. Raw Materials**

The important raw materials for the manufacture of HPMC are as follows: pulp (cellulose), methyl chloride, propylene oxide, caustic soda solution, acid, buffering agent, and water.

Methyl chloride is a colorless, odorless 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.

Propylene oxide (PO) is a highly reactive chemical. The appropriate amount of PO is transferred to the cellulose reactor as required and the transfer is monitored with instruments to assure proper operation.

Pulp (cellulose) is received and ground in the grinders. It 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.

Acid is used in the production of low viscosity products in the LV reaction. Residual acid is neutralized with a buffering agent.

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

## 2. Reaction

Pulp is added to the reactor followed by caustic soda solution to produce alkali cellulose. The appropriate amounts of other raw materials are then added to produce the desired type of HPMC in accordance with the product recipes. The resulting slurry is transferred to the wash step.

## 3. Washing

The slurried material is transferred to a series of filters to wash the sodium chloride and residual organics from the HPMC material. HPMC is purified by washing with hot water. Small soluble portions of hemicellulose ethers, degraded short-chain oligomers and low molecular weight glycol ether byproducts are extracted along with the salt into the wastewater. Any residuals or unreacted raw materials such as methyl chloride or propylene oxide are also removed in this washing step. To ensure proper removal of salt and organics from the HPMC, process variables are monitored.

## 4. Drying

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

## 5. Size Reduction

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

6. Batch Homogenization

As a result of the product variation imposed by the use of a natural raw material (pulp), and the batch-to-continuous-to-batch nature of this process, it is necessary to mix our final batches in blenders prior to packaging to assure homogeneity.

7. HPMC Lower Viscosity Products

Some of the HPMC products produced are intentionally subjected to acid in order to lower the final viscosity of the product. The reaction is monitored to obtain the desired viscosity. A buffering agent is used to neutralize the acid at the end of the reaction.

A. Production Instructions

Written manufacturing instructions are maintained in each production facility. These give the steps necessary to produce, trouble shoot and analyze all aspects of the production of HPMC.

Because unit operations within the production facility are monitored via a computer system, most of the actual recipe instructions are within the computer scheme itself. Within the computer program are all the set points and control parameters. The computer allows for collection of in-process data and enables Operations personnel to continuously monitor the actual events versus the predicted/theoretical. Documentation from the computers to support decisions made by Operations personnel is available for each final batch of HPMC produced.

B. In-Process Sampling

In-process sampling is conducted based on an established sample plan to monitor product properties and process parameters on a routine basis. The data are used to make changes to the process if necessary and to support product release.

C. Final Product Sampling

Once the product is packaged, a representative sample is acquired and sent to the Quality Control Lab for a final product analysis. All HPMC products have written specifications.

## Appendix D

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**Appendix E**

## Conclusion of the GRAS Panel Review of

### Hydroxypropyl Methylcellulose

We have reviewed the scientific evidence contained in The Dow Chemical Company's generally recognized as safe notification (GRASN) for hydroxypropyl methylcellulose (HPMC), dated August 21, 2006. Based on our independent and collective critical evaluation of the information and data summarized in the GRASN, we conclude that HPMC, meeting the specifications described in the GRASN and used in accordance with good manufacturing practice (GMP), is generally recognized as safe by scientific procedures for use as a food ingredient.

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Michael W. Pariza, Ph.D.  
Michael W. Pariza Consulting, LLC  
Madison, Wisconsin

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~~Joseph F. Borzelleca, Ph.D.~~  
Emeritus Professor, Dept Pharmacology &  
Toxicology  
Virginia Commonwealth University  
Richmond, Virginia

---

~~Herbert Blumenthal, Ph.D.~~  
Silver Spring, Maryland

AM

**Garcia, Edmundo**

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**From:** Drozen, Melvin S. [Drozen@khlaw.com]  
**Sent:** Tuesday, September 26, 2006 1:57 PM  
**To:** Garcia, Edmundo  
**Cc:** Mathews, Robert A.; Hill, Devon W.  
**Subject:** Hydroxyl Propyl Methylcellulose(HPMC) GRAS Notification

Dear Dr. Garcia:

This will confirm our discussion today. With regard to Dow's GRAS Notification for HPMC, all of the data and information that are the basis for the GRAS determination are available for the Food and Drug Administration's review and copying or will be sent to FDA upon request.

Thank you for calling this matter to our attention. Please let us know ASAP if for any reason this email confirmation is not sufficient.

Sincerely,

Mel Drozen.

---

This message and any attachments may be confidential and/or subject to the attorney/client privilege or otherwise protected from disclosure.

If you are not a designated addressee (or an authorized agent), you have received this e-mail in error, and any further use by you, including review, dissemination, distribution, copying, or disclosure, is strictly prohibited. If you are not a designated addressee (or an authorized agent), we request that you immediately notify us of this error by reply e-mail and then delete it from your system.

9/26/2006

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**SUBMISSION END**

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## *Reference List for Industry Submission, GRN 000213*

<i>Pages</i>	<i>Author</i>	<i>Title</i>	<i>Publish Date</i>	<i>Publisher</i>	<i>BIB_Info</i>
000042 - 000043	NA	Hydroxypropyl Methylcellulose	NA	Food Chemicals Codex	NA
000044 - 000047	NA	Hypromellose	NA	USP-NF Monograph	NA
000050 - 000051	Committee on National Formulary	Hydroxypropyl Methylcellulose	1965	The National Formulary	Twelfth Edition

*NA- Not applicable*

AM

**Hendrickson, Carrie**

---

**From:** Drozen, Melvin S. [Drozen@khlaw.com]  
**Sent:** Monday, February 26, 2007 10:04 AM  
**To:** Hendrickson, Carrie  
**Cc:** Hill, Devon W.; Mathews, Robert A.; Kozuch, Maureen (ME); Treble, Imogene (IE)  
**Subject:** RE: HPMC--FDA Questions/Requests  
**Attachments:** EDI FDA response.doc

Dear Dr. Hendrickson:

This responds to your questions/requests regarding the Dow Chemical Company's GRAS Notice no. 000213 for hydroxypropyl methylcellulose(HPMC)--

1. You requested that we provide information on an Estimated Daily Intake(EDI). Per your request, and as you suggested, attached is an EDI estimate and discussion consistent with what we provided to you prior to our June 2006 meeting. Again, the EDI is based on potential or example uses, and of course we have requested and believe the data fully support our conclusion that HPMC is GRAS for use in foods generally up to 20 grams/day. You indicated in our phone discussion that you understood all of this and that FDA's responsive letter would make all of this clear.
2. You requested information on the conditions under which the high(over greater than or equal to 1500 centipoise) and low viscosity(less than 1500 centipoise) ranges were determined. Dow informs us that viscosity is measured at a temperature of 20 degrees C using a solution of 2 wt. %.
3. Your last question requested information on the reasons for the variations in residue of ignition specifications presented by the Company's specifications and in the various referenced monographs. We understand that the variation in residue on ignition is caused by residual salt content of the product, an unavoidable by-product of the manufacturing process. The salt is generated during the manufacturing process and is substantially removed during the washing step of the process. There is some variability in each of these processes. Parameters are monitored to ensure that the residue on ignition specification is met.by the manufacturing or washing process.

Please let us know if, for any reason, you need further information. If not, we are hopeful that we will receive a positive FDA response to the GRAS notice very soon.

Best regards,

Mel Drozen.

Melvin S. Drozen  
tel: 202.434.4222 | fax 202.434.4646 | drozen@khlaw.com  
1001 G Street, N.W., Suite 500 West | Washington, D.C. 20001

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## Estimated Daily Intake

### Summary:

Using food consumption estimates for the total U.S. population from the USDA survey, Dow calculates the estimated daily intake (EDI) to be 18.05 grams of HPMC per day for the example intended uses, including its use as a source of dietary fiber (Table 1 attached). While Dow believes the expected categories of use and concentrations of HPMC used in these categories are reasonable numbers as examples, the calculated value of the total mean intake of HPMC is higher than what would actually occur.

This calculated value of the total mean intake of HPMC is believed to be higher than what would actually occur for several reasons.

- 1) Recommended fiber consumption in the United States is 20-30 grams of fiber a day. It would be highly unlikely for an individual to consume 18.05 grams of fiber solely from HPMC per day.
- 2) The calculation assumes that every product in all categories will use HPMC. It is highly unlikely that this will happen. The food survey data from USDA contains a variety of foods in the assigned categories. Only a small percentage of the foods in each category would be expected to contain HPMC. Based on Dow's technical experience, examples of foods where HPMC might be added are noted in Table 1. For example, under the egg category, HPMC could be expected to be used in egg white substitutes and omelet mixes. HPMC would not be used in whole fresh eggs, which probably is the main area of consumption of this category.
- 3) The calculation assumes 100% market penetration in all categories and for all products. There are many different ingredients and additives that compete for the functional effects provided by HPMC. It is highly unlikely that HPMC would be the additive of choice for all food products in all categories.

### Food Data:

Data from USDA's 1994-96 Continuing Survey of Food Intakes by Individuals and 1994-96 Diet and Health Knowledge Survey were used to estimate food consumption in the various food categories. Tables 9.1 through 9.7 were used to give mean quantities (in grams) of foods consumed by individuals.

Dow has estimated the potential future consumption of products containing HPMC in Table 1. The estimates are based on the assumption that consumption of HPMC will be self-limiting (due to product characteristics such as mouth feel, texture, and off flavor).

**Calculation:**

Calculations are done for the EDI based on the proposed fiber use. The calculation of HPMC estimated daily intake (i.e., daily consumption) is:

HPMC consumed for each food category (gram/day) = Mean quantity of food consumed per category (g/d) x proposed upper limit of HPMC (%)

The EDI is the sum for all USDA food groups containing HPMC.

**Results:**

The EDI based on fiber use is 18.05 grams per day of HPMC, as shown in Table 1 assuming 100% market penetration for all food products. The EDI estimates are based on the best available information. The 1994-96 Continuing Survey of Food Intakes by Individuals and 1994-96 Diet and Health Knowledge Survey were used to estimate food consumption in the various food categories. The fraction of HPMC in food is based on the proposed use level.

**Summary:**

This EDI calculation estimates the daily intake for HPMC using a USDA study for food consumption and the proposed use levels of HPMC in food. Dow expects that the consumption of HPMC as a source of fiber will be self-limiting.

**Table 1 Future Use - A summary of the USDA food categories and a calculation of EDI for HPMC.**

HPMC Estimated Daily Intake (EDI) Calculation for Future Use				
Table # in USDA Table Set 10	Product	Mean Quantity Consumed per Individual (grams)	Proposed use level (%)	HPMC(g/day)
Table 9.1. Grain products	Yeast, breads, and roll i.e. white breads with fiber added	50	5.0%	2.50
	Cereals and pasta/Ready-to-eat-cereals i.e. breakfast cereals	16	5.0%	0.80
	Cereals and pasta/Pasta i.e. fiber added pasta	18	2.0%	0.36
	Quick breads, pancakes, french toast i.e. tortillas, french toast	19	5.0%	0.95
	Cakes, cookies, pastries, pies i.e. doughnuts, pound cake, pie filling, granola bars	38	5.0%	1.90
	Mixtures mainly grain i.e. pizza, frozen meals that are mainly grain/pasta	109	2.0%	2.18
Table 9.3. Fruits	Citrus juices	60	2.0%	1.20
	Noncitrus juices and nectars	27	2.0%	0.54
Table 9.5. Meat, poultry, and fish	Fish and shellfish ie. fish sticks and fish balls	10	2.0%	0.20
	Mixtures mainly meat, poultry, fish i.e. frozen dinners, canned pasta	99	5.0%	4.95
Table 9.6. Eggs; legumes; nuts and seeds; fats and oils; sugars and sweets:	Eggs i.e. omelets, egg white substitute	18	4.0%	0.72
	Legumes i.e. veggie burgers, meat substitutes	25	5.0%	1.25
	Nuts and seeds i.e. peanut butter	4	2.5%	0.10
	Sugars i.e. sugar substitutes	3	1.5%	0.05
	Candy ie. candy bars, fruit roll ups	7	5.0%	0.35
				<b>18.05</b>