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January 11, 2006

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FOOD ADDITIVE SAFETY

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Via Hand Delivery

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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 Agency 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. 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.

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

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

January 11, 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, by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), and the regulations of many countries.
- The production of HPMC as practiced by Dow.
- Analytical methodology, included by reference to the Food Chemicals Codex, and JECFA.
- Estimated exposure; inferred by the breadth of current international approved uses of HPMC as a food additive and a calculation of the Estimated Daily Intake (EDI) on use 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, generally, for multiple technical effects and as a dietary fiber in foods.

Dow markets HPMC under the METHOCEL* brand name.

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, including meat products, for multiple technical effects and as a dietary fiber in foods.

* Trademark of The Dow Chemical Company.

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

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. International Clearances for HPMC are provided in Appendix G.

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 number 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.

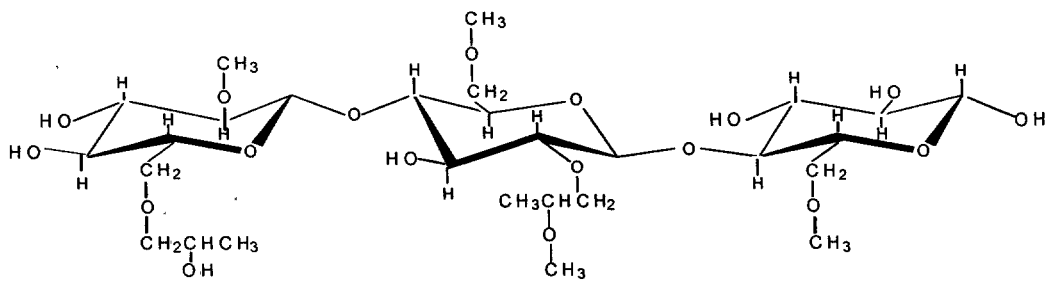
II. Detailed Information about the Identity of the Notified Substance

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 name:	Hypromellose, synonyms: hydroxypropyl methylcellulose,
Japanese Pharmacopeia	Hypromellose

name:
INS number: 464
Synonyms: Hypromellosum
RTECS number: NF9125000

2. Substitution Range:

This notification proposes to expand the currently recognized range of methyl and hydroxypropyl groups described in the various monographs for food-grade or pharmaceutical-grade HPMC. Dow has concluded that all combinations of methyl and hydroxypropyl groups are GRAS for HPMC containing 16-31.5% methyl groups and hydroxypropyl groups up to and including 32%, but greater than zero. Percentages refer to the quantity of substitutions on a weight basis relative to the product in question. As discussed more fully below, the scientific literature supports the proposition that HPMC and all other modified celluloses, including cellulose itself, have virtually no toxic effects due primarily to the fact that these large molecular weight ingredients are not significantly absorbed from the gastrointestinal system. Thus, the systemic toxicity of HPMC does not depend on the type and/or degree of the substitution. Appendix A includes the references for all the current specifications for HPMC; the current FCC specifications, the current JECFA specifications and the original National Formulary (NF) specifications.

The substitution description in the Food Chemicals Codex Fifth Edition (FCC) monographs for cellulose gum, also known as sodium carboxymethyl cellulose (CMC), and hydroxypropyl cellulose (HPC) illustrate this approach. In each of these compositions, the allowed substitutions simply cover a large range of substitutions from zero to some upper limit; manufacturers can make and sell products within this wide range of allowed % carboxymethyl or % hydroxypropyl substitution.

3. Physical Description: white/off-white powder

4. 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 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 hydroxypropyl methylcellulose products, propylene oxide is used in addition to methyl chloride to obtain hydroxypropyl substitution on the anhydroglucose units. This substituent group, –OCH2CH(OH)CH3–, contains a secondary hydroxyl on the number two carbon and may also 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 C for details on the manufacture of HPMC by Dow and Appendix B for a process flow diagram which details the scheme for the production of HPMC.

Dow HPMC is manufactured in compliance with the requirements of the USP, NF and FCC. Good manufacturing practices (GMP) for the production of HPMC are followed.

5. Composition and Specifications

The specifications of food-grade HPMC are well-defined by monographs in the Food Chemicals Codex and by JECFA. Copies of the current monographs are appended to this notification in Appendix A.

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. The types of variables and the limits are 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°C 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.

6. 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.

Test Requirements – Food-grade HPMC meets the specifications for purity as provided by the Food Chemicals Codex and the FAO/WHO Joint Expert Committee on Food Additives.

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

1. Applications and Intake Estimate

a. Foods in Which Used and Purpose of Use

HPMC is intended for use as a direct human food ingredient and is added to foods as a color stabilizer, dough strengthener, emulsifier, firming agent, formulation aid, binder, lubricant and release agent, nutrient supplement, stabilizer and thickener, surface-active agent, synergist, and texturizer as defined in 21 CFR § 170.3(o) below:

(4) "Colors and coloring adjuncts": Substances used to impart, preserve, or enhance the color or shading of a food, including color stabilizers, color fixatives, color-retention agents, etc.

(6) "Dough strengtheners": Substances used to modify starch and gluten, thereby producing a more stable dough, including the applicable effects listed by the National Academy of Sciences/National Research Council under "dough conditioner."

(8) "Emulsifiers and emulsifier salts": Substances which modify surface tension in the component phase of an emulsion to establish a uniform dispersion or emulsion.

(10) "Firming agents": Substances added to precipitate residual pectin, thus strengthening the supporting tissue and preventing its collapse during processing.

(14) "Formulation aids": Substances used to promote or produce a desired physical state or texture in food, including carriers, binders, fillers, plasticizers, film-formers, and tableting aids, etc.

(18) "Lubricants and release agents": Substances added to food contact surfaces to prevent ingredients and finished products from sticking to them.
(20) "Nutrient supplements": Substances which are necessary for the body's nutritional and metabolic processes.
(28) "Stabilizers and thickeners": Substances used to produce viscous solutions or dispersions, to impart body, improve consistency, or stabilize emulsions, including suspending and bodying agents, setting agents, jellying agents, and bulking agents, etc.
(29) "Surface-active agents": Substances used to modify surface properties of liquid food components for a variety of effects, other than emulsifiers, but including solubilizing agents, dispersants, detergents, wetting agents, rehydration enhancers, whipping agents, foaming agents, and defoaming agents, etc.
(31) "Synergists": Substances used to act or react with another food ingredient to produce a total effect different or greater than the sum of the effects produced by the individual ingredients.
(32) "Texturizers": Substances which affect the appearance or feel of the food.

b. Level of Use

Appendix D contains Table 1 which presents information on self-limiting concentrations of use for HPMC. The technical effect upper limits for the incorporation of HPMC into food categories as commonly described and referenced in 21 CFR § 170.3(n)(1)-(43) are presented. 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. Effects that can occur when 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, therefore, are self limiting.

c. Estimated Daily Intake

Summary:

Using food consumption estimates for the total U.S. population, the best approximation of the estimated daily intake (EDI) is 5.50 grams of HPMC per day for the intended uses, including its use as a source of dietary fiber. (See Appendix E, Table 2.)

Non-Toxicity:

HPMC exerts functional changes in food products without undergoing or initiating chemical changes that would alter the nutritional value of the food products. HPMC can

provide this functionality at very low concentrations. *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.

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 (Appendix E). 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 (%) x products containing HPMC (%)

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

Results:

The EDI based on fiber use is 5.50 grams per day of HPMC, as shown in Table 1 (see Appendix E). 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 upper limit. The estimated market share of products containing HPMC is based on the best estimate by Dow.

Summary:

This EDI calculation estimates the daily intake for HPMC using a USDA study for food consumption and the proposed upper limits of HPMC in food. Some judgment is required in estimating the fraction of a food group that contains HPMC because all foods

do not contain HPMC. Dow expects that the consumption of HPMC as a source of fiber will be self-limiting.

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).

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 35th meeting. A Group ADI of "not specified" for modified celluloses established at the 35th 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 HPMC and other modified celluloses, as discussed below, supports this interpretation of the data.

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.

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

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

Acute Oral Toxicity

HPMC

The acute oral toxicity for HPMC has been evaluated in two studies. LD_{50} 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 ([2]Hodge *et al.,* 1950) were reported.

Analogues

A number of acute oral toxicity studies on modified cellulosics have also demonstrated the relatively low oral toxicity of this family of compounds. Oral LD_{50} values in rats (sex and strain not reported) for hydroxypropyl cellulose of 10,200-15,000 mg/kg/day ([12]IBL, 1964; [13]Kitagawa *et al.,* 1976a), ethylhydroxyethyl cellulose of 5000-10,000 mg/kg/day ([17]Cuthbert *et al.,* 1975), and ethyl cellulose of 5000 mg/kg/day ([47]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_{50} values were reported by [2]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 ([3]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) ([47]Moreno, 1977). The LD_{50} was reported to be greater than 5000 mg/kg/day. Dermal irritancy of hydroxypropyl cellulose has also been evaluated in human subjects ([14]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.

[8]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.

[2]Hodge *et al.* (1950) conducted a 30-day dietary toxicity study containing 0, 2, 10 or 25% HPMC 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.

[5]McCollister *et al.* (1961) evaluated the potential toxicity of HPMC 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 was evaluated in two 90-day studies in rats. [6]McCollister & Copeland (1967), [7]McCollister *et al.* (1973), and [7a]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. 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.

[9]Schwetz *et al.* (1973) also found no adverse effects of low viscosity (4.22cP) HPMC 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.

[4]McCollister & Oyen (1954) fed male and female rats of Wistar lineage diets containing 0, 1, 3, 10 or 30% HPMC 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.

[2]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. [2]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. [9a]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. [7]McCollister *et al.* (1973), and [9]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 ([12]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 ([16]Kitagawa *et al.*, 1978b).

Ethylhydroxyethyl cellulose was evaluated in a 90-day dietary toxicity study in male and female CD rats ([18]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 ([24]Bauer *et al.*, 1944; [25]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 ([23]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 ([26]Ellingson and Massengale, 1952; [27]Hall and Hall, 1962; [28]Fitch *et al.*, 1962; [29]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 ([30]Bauer, 1975).

Genetic Toxicity

HPMC

HPMC has not been directly evaluated in genetic toxicity testing; however, the methyl cellulose analogue has been found to be negative in a variety of assays.

Analogues

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

Carcinogenicity

HPMC

[2]Hodge *et al.* (1950) evaluated HPMC 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 ([45]ICI, 1961), or up to 5% methyl cellulose in male and female Sprague Dawley rats ([7]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 was found to have no effect on "the reproductive ability of the F1 offspring were obsd [observed]" at dose levels as high as 5000 mg/kg/day in rats (strain unspecified) ([15]Kitagawa *et al.,* 1978a). Mean litter weights and pre-implantation loss were increased in rats and rabbits at the 5000 mg/kg/day dose level. Hydroxypropyl cellulose was also found to have no effect in Himilayan rabbits at doses administered orally up to 5000 mg/kg/day ([16]Kitagawa et al., 1978b). Methyl cellulose has been evaluated for developmental toxicity in female mice, rats, and rabbits (strains not reported) in several studies ([35]Cannon Labs, 1975; [36]1977; [34]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 ^{14}C-HPMC labeled in the methoxyl position by methyl capping of the hydroxypropyl groups. In male and female Sprague-Dawley rats administered 500mg of ^{14}C-HPMC as single or repeated bolus doses, greater than 98% of administered ^{14}C was excreted via the feces in the absence of any appreciable biliary excretion ([10]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 ^{14}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 ^{14}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 ([8]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 ^{14}C-hydroxyethyl cellulose as noted for HPMC was demonstrated in male and female CDF rats ([50]Sullivan *et al.*, 1968a) and in male and female CDF rats and dogs (sex and strain not reported) ([51]Sullivan *et al.*, 1968b). Methyl cellulose has also been reported to be excreted nearly exclusively via the feces within 48 hours ([37]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 in doses ranging from 0.6-8.9g on three separate occasions ([11]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 ([19]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 ([22]Tainter, 1943, 3 persons; [30]Bauer, 1975, unspecified number; [39]Schweig, 1948, 37 persons; [40]Bargen, 1949, unspecified number; [41]Crane *et al.*, 1969, two persons; [42]Eastwood *et al.*, 1988, five males; [43]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	[1]LD_{50} in rats > 1000 mg/kg 2[1]LD50 in rats > 4000 mg/kg	[12,13]LD_{50} in rats = 10,200-15,000 mg/kg	[17]LD_{50} in rats = 5000-10000 mg/kg	[20]In man, single oral doses of 5g and 10g were well tolerated.		[48]LD_{50} in rats = 5000 mg/kg
Acute Dermal Toxicity						[48]LD_{50} in rabbits > 5000 mg/kg
Acute Toxicity-Other Routes	[2]LD_{50} IP in rats = 5000 mg/kg [2]LD_{50} IP in mice = 5000 mg/kg			[21]In dogs, single IV injection of 40 mL of 0.7-2.8% solutions in saline - anemia, leucopenia and increased sedimentation rate.		
Dermal Irritation	[3]Repeated Rabbit dermal irritation study (10 applications	[14]Repeated human patch testing (50 subjects, 10	[17]In abraded skin of albino rabbits, very mild irritant			

	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		[14]Repeated human patch testing (50 subjects, 10 repeated patches of 10% aqueous solution plus rechallenge) resulted in no sensitization.	[17]Negative in the guinea pig by Kligman's maximization test.			
Repeated-Dose Toxicity	[4-8]Up to 121-day dietary studies in rats: up to 30% in diet. Mortality and decreased bodyweight noted at 25% and 30% doses	[12]90-day dietary study in rats = increased food consumption at high dose only (~5000 mg/kg/day) [13]6-month	[18]90-day dietary study in rats = decrease in liver relative weights, no histopathologic correlate at 2500 mg/kg/day	[23]95-day dietary study in rats up to 10% in diet = no significant findings. [23]8-month drinking water	[44]Data from short-term tests indicate that 3g daily in the diet had no effect in rats.	[48]NOEL > 182 mg/kg/day

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	but only decreased body weight at 20% or lower doses. No histopathological changes noted. [2]Up to 25% in diets of rabbits for 30 days, no findings noted. [7,9,9a]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.	dietary study in rats = decreased hemoglobin at 6000 mg/kg/day	(highest dose tested).	study in rats up to 1% in water = no significant findings. [24,25]6&8-month dietary studies in rats up to 5% in diets = no significant findings. [25]90-day diet study in rats up to 50% in diet = no significant findings. [26-29]10-112 day IP/IV studies in rats (1-2.5% solutions) = increased spleen weight, MC deposits in renal glomeruli, arterial hyper-tension. [30]4-week dog dietary study		

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				up to 100g daily = no significant findings.		
Genetic Toxicity	[9b]Negative cytogenetics (chromosome aberration) assay of bone marrow cells from rats administered up to 5% HPMC for 90 days.			Negative in [31,32]AMES, [33]reverse mutagenesis, [33]mitotic recombination, [32]chromosomal aberration, [33]C.A. induction, [33]dominant lethal assays.		
Carcinogenicity	[2]Up to 20% in diet of rats, negative for carcinogenicity			[7]2-year dietary study in SD rats up to 5% in diet = negative	[45]2-year dietary study in rats and mice up to 1% in diet = negative [44]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	[5,6,7,9] Lack of gonadal toxicity in several subchronic repeated dose studies in males and females of several species.	[15]At 5000 mg/kg/day in rats, no effect on progeny reproduction.		[34]Reduced pregnancy rate in surviving high-dose females (1600 mg/kg/day), increase in resorption rates.		
Developmental Toxicity		[15,16]At 5000 mg/kg/day in rats & rabbits, an increase in mean litter weight & % pre-implantation loss.		[35]Non-teratogenic in mice. [34,36]Non-teratogenic in rats; increased centers of ossification in ribs of rat fetuses. [34]Non-teratogenic in rabbits.		
Pharmacokinetics & Metabolism	[10]>99% excreted in feces after a single bolus dose. After 5 repeated doses,	[12,13]98.32% - 102.7% of ingested material is excreted in the		[37]102.2% of a bolus dose of 500 mg/kg was excreted via feces within 48	[46]90% of a single 0.6g dose recovered in feces by 96 hours.	

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

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d. Possible Residuals and Risk Assessment

The risk assessment described below provides an estimation of safe levels of three specific residual impurities that may, in theory, be found in HPMC: propylene oxide and two chloropropanols, 3-chloro-1,2-propanediol (MCPD) and 1,3-dichloro-2-propanol (DC2P). JECFA reviewed the safety of MCPD and DC2P in 1993 for the specific purpose of determining the safety of hydrolyzed vegetable protein, a common food ingredient.[52] JECFA reviewed the toxicology of MCPD again in 2001.[56] In a preliminary analysis in 1997 of data from two unpublished carcinogenicity bioassays of MCPD and DC2P, FDA concluded that evidence available at that time indicated that the two chloropropanols displayed carcinogenic activity in rats.[53] FDA has published an evaluation of propylene oxide as part of the risk analysis associated with adjuvants, production aids, and sanitizers used in the manufacture of indirect additives.[57]

3-Monochloro-1,2-propanediol

The most recent expert panel reviews of MCPD indicate that it is neither genetically toxic, mutagenic, or carcinogenic as measured by *in vivo* assays. In 2000, the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) of the UK, reviewed new data specifically to evaluate the potential for MCPD to induce genetic effects *in vivo*. COM concluded that the most recent data on MCPD established that it had no significant genotoxic potential *in vivo*.[54] After considering this advice and available carcinogenicity data, the UK's Committee on Carcinogenicity (COC) concluded that MCPD was unlikely to present a carcinogenic risk to humans provided exposure was 1000 fold lower than the NOEL of 1.1 mg/kg bw/day in rats (i.e., a safe intake is 1.1 μg/kg bw/day).[55]

In a toxicological evaluation of MCPD in 2001 JECFA adopted a provisional tolerable daily intake (PTDI) of MCPD of 2 μg/kg bw/day, based on the Committee's opinion that 1.1 mg MCPD/kg bw/day was a lowest observed effect level (LOEL) and then applying a safety factor of 500.[56] In the pivotal long-term study [used for setting the ADI] in Fisher 344 rats, the absolute weight of the kidneys were significantly increased in exposed animals. At all doses tested, the incidence of tubule hyperplasia in the kidney (the pivotal target organ) was higher than in the controls. The Committee concluded that the lowest exposure, 1.1 mg/kg bw/day was a LOEL because of a significant dose-response relationship (Even though this dose did not induce a statistically significant effect.). The Committee established a PTWI of 2 μg/kg bw/day applying a safety factor of 500 to the LOEL for kidney hyperplasia. The safety factor was considered to be adequate to account for the effects on male fertility and for inadequacies in the reproductive toxicity database.

The JECFA Toxicological Monograph also concluded that: Repeated doses of MCPD in excess of 1 mg/kg bw/day in male rats decreased sperm motility and impaired fertility. An exposure of 1 mg/kg bw/day was a NOEL for spermatological effects in male rats as shown in two separate studies.[59]

With specific regard to the carcinogenicity of MCPD, JECFA concluded: Altogether, four long-term studies of toxicity and carcinogenicity were available; three (two with mice and one with rats) did not meet modern standards of quality. Nevertheless, none of the three studies indicated carcinogenic activity. In the fourth study, conducted in Fischer 344 rats, MCPD was associated with increased incidences of benign tumors in some organs. These tumors occurred only at doses greater than those causing renal tubule hyperplasia, which was selected as the most sensitive end-point.

It is apparent that all currently available data on the toxicology of MCPD has been thoroughly reviewed by expert panels of toxicologists. The UK's Committee on Carcinogenicity adopted a tolerable intake level of 1 μg/kg bw/day and JECFA adopted a provisional tolerable daily intake of 2 μg/kg bw/day. For the purpose of this GRAS notification, Dow has adopted the lower value to assure the safe use of HPMC as an ingredient in food.

1,3-Dichloro-2-propanol

The carcinogenicity and mutagenicity of two dichloropropanols (1,3-DCP, 2,3-DCP) was evaluated by working groups of the European Commission in 2004. No carcinogenicity study is available for 2,3-DCP The Committee on Mutagenicity (COM) concluded that 1,3-DC2P and 2,3-DC2P are not genotoxic *in vivo*, although positive *in vitro* genotoxicity has been reported.

The UK's Committee on Carcinogenicity (COC) reviewed the same data on genotoxicity and the data on carcinogenicity. The COC concluded that the *in vivo* data for 1,3-DCP indicated that the liver carcinogenicity reported could be attributed to a non-genotoxic hepatotoxic effect. However, the tumors of the tongue reported for 1,3-DCP could not be ruled out as due to a genotoxic effect. Therefore, for the purposes of this risk assessment, and until further data become available, risks due to exposure to 1,3-DCP will be evaluated by a linear extrapolation from the lowest exposure resulting in a statistically significant excess of tongue tumors in male rats (the procedure used by FDA).

Based on data available to us obtained though the Freedom of Information Act we have determined that the unit risk for tongue tumors in male rats determined from a drinking water exposure of two years duration is 0.012 per mg/kg bw/day. This unit risk factor was calculated from a combined total of benign and malignant tumors in the male rats of 24% at an exposure rate of 20 mg/kg bw/day. The calculation is 0.24/20 mg/kg bw/day = 0.012 per mg/kg bw/day. Using FDA's reference risk of one in one million as an insignificant risk of exposure to residual impurities that are carcinogenic, the virtually safe dose (VSD) for 1,3-DCP is calculated as:

$$10^{-6}/0.01 \text{ per mg/kg bw/day} = 100 \times 10^{-6} \text{ mg/kg bw/day or } 0.1\ \mu\text{g /kg bw/day.}$$

Based on FDA's reference body weight of 60 kg, the VSD for 1,3-DCP is <u>6 μg per day</u>.

Propylene Oxide

FDA's VSD for exposures to propylene oxide as a dietary contaminant is 1.4 micrograms per person per day calculated from a 1991 *Federal Register* notice.[58]

Maximum Permissible Levels of Chloropropanols and Propylene Oxide in HPMC

Based on the above risk assessments, the following maximum permissible levels of the two chloropropanols and propylene oxide, as residual contaminants are calculated as follows.

MCPD

The safe daily intake of MCPD was calculated above as 60 μg/day; the 90th percentile intake of HPMC, estimated as twice the average intake of 5.5 grams per day, is 11 grams per day. Therefore the maximum permissible residual level of MCPD in HPMC is 0.06 ppm
(60 μg /day ÷ 11 g/day = 5.5 μg MCPD/g HPMC, i.e., 5.5 ppm).

DC2P

The VSD for 1,3-DC2P estimated above is 6 μg /day. Therefore, the maximum permissible residual level of DC2P in HPMC is 0.55 ppm (6 μg /day ÷ 11 g/day = 0.55 μg DC2P /g HPMC, or 0.55 ppm = 550 ppb).

Propylene Oxide

FDA's VSD for exposures to propylene oxide as a dietary contaminant is 1.4 μg per person per day. Therefore, the permissible residual level of propylene oxide in HPMC is 0.130 ppm (1.4 μg /day ÷ 11 g/day = 0.13 μg propylene oxide/g HPMC, 0.13 ppm, or equivalently 130 ppb).

Levels of propylene oxide were measured in eleven lots of product. The detection limit of PO was calculated to be 21 ppb per gram of HPMC. No detectable amount of propylene oxide was present in any of the eleven samples analyzed. The analysis for this contaminant was performed as an additional demonstration of safety.

According to manufacturing process information for propylene oxide, 3-chloro-1,2-propanediol is formed during the process but is left in the hydrolizer bottom effluent when the propylene oxide is stripped. 1,3-dichloro-2-propanol has not been found in the hydrolizer bottom stream. The producer does not regard these two components as potential impurities in propylene oxide and does not analyze for them.

Conclusions

Based on the above discussions of the available toxicological data and reviews of the available data by expert panels, Dow has adopted the following measures of daily intake of each residual and for the levels of each residual in HPMC. The safe levels of intake and maximum permissible levels in the HPMC products are based on a 90th percentile intake of 11 grams of HPMC per day (estimated as twice the average intake; calculations provided below) and the conclusions regarding safe exposure levels adopted by the expert panels or agencies that have reviewed the residual contaminants, consistent with FDA's approach to risk assessment of potential contaminants in food ingredients.

Contaminant	Safe Intake Level	Safe Level in HPMC
3-Chloro-1,2-propanediol (MCPD)	60 μg per day	5.5 ppm
1,3-Dichloro-2-propanol (DC2P)	6 μg per day	0.55 ppm
Propylene Oxide	1.4 μg per day	0.13 ppm

These measures of safe human exposures reflect the most recent conclusions of expert toxicological panels.

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, whose use should be limited only by good manufacturing practice.

Respectfully submitted,

Dr. Imogene Treble
Environment Health &
Safety Regulatory Leader
The Dow Chemical Company

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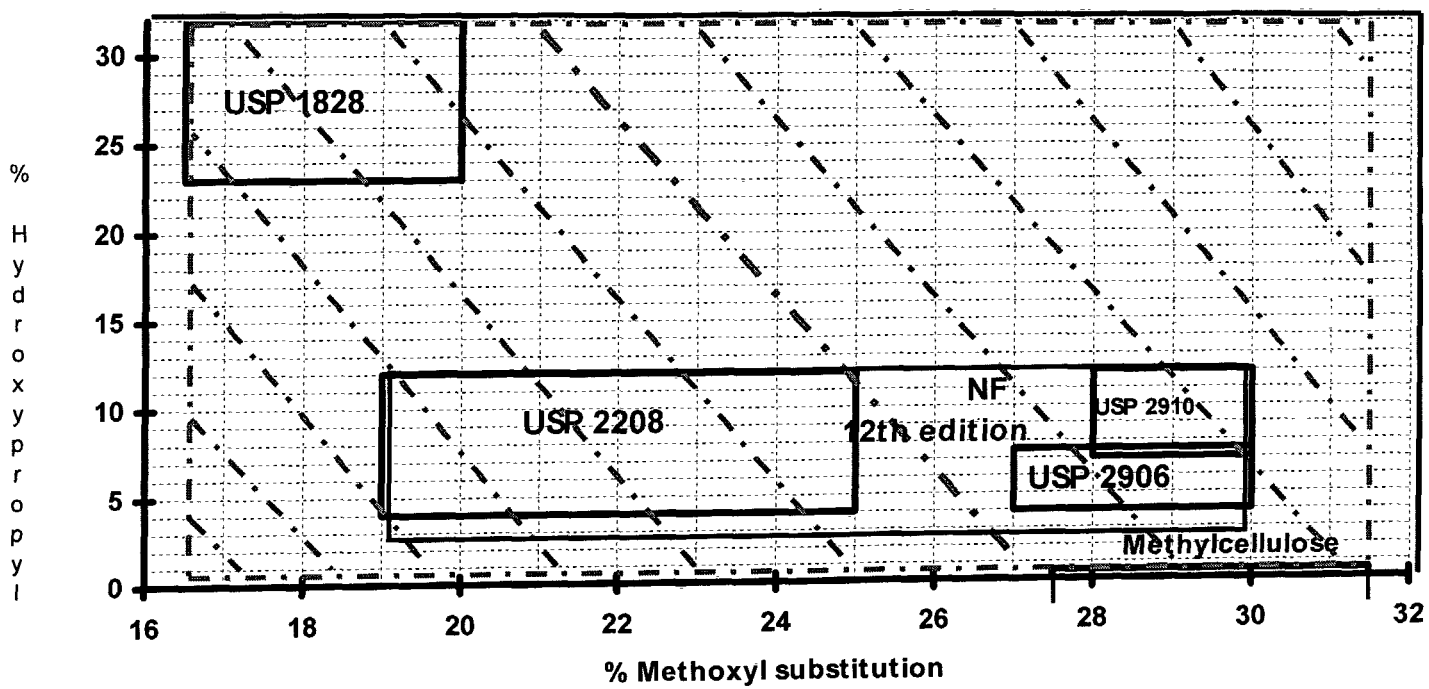
Appendix A

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



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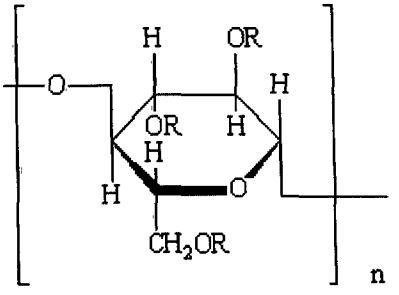
HYDROXYPROPYLMETHYL CELLULOSE

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	[C6H7O2(OH)x(OCH3)y(OCH2CHOHCH3)z]n where z = 0.07 - 0.34 y = 1.12 - 2.03 x = 3-(z + y): (z + y = degree of substitution)
STRUCTURAL FORMULA	 where R = H or CH3 or CH2CHOHCH3
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 methoxylgroups (-OCH3) and not less than 3% and not more than 12% hydroxypropoxyl groups (-OCH2CHOHCH3), 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)

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:

Amount (mg/kg) =

$$\frac{(H: 1\text{-}CP)_{sample}}{(H: intern.\ stand.)_{sample}} \times \frac{(H: intern.\ stand.)_{stand\,soln}}{(H\ 1\text{-}CP)_{stand\,soln}} \times \frac{8.5 \times 6.0}{W}$$

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 155o and the desired heating rate may be maintained. The distillate is collected in a 150-ml beaker, G, or other suitable container.

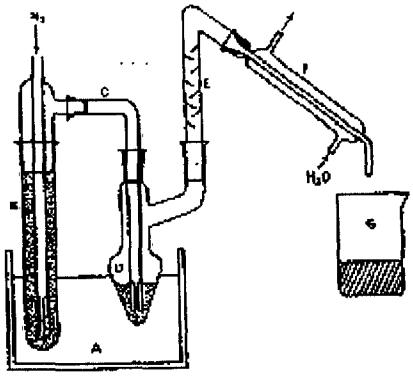


Figure Apparatus for Hydroxypropyl Determination

Procedure

Transfer about 100 mg of the sample, previously dried at 105o for 2 h and accurately weighed, into the boiling flash, 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 155o 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, Va 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 Ya.

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, Vb/Yb= 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 methylcellulose (containing no foreign material) in place of the sample, recording the average volume of 0.02 N sodium hydroxide required as Vm and the average volume of 0.02 N sodium thiosulfate required as Ym.

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
N1 = the exact normality of the 0.02 N sodium hydroxide solution
N2 = the exact normality of the 0.02 N sodium thiosulfate solution
k = VbN1/YbN2

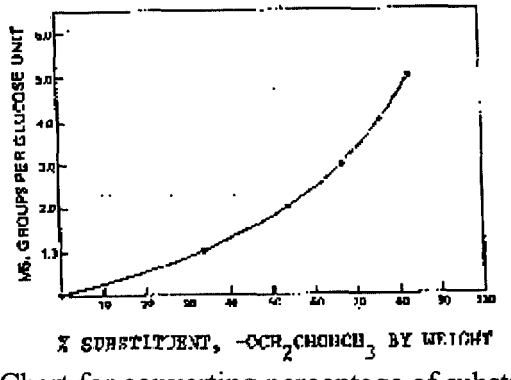


Chart for converting percentage of substitution, by weight, of hydroxypropoxyl groups to molecular substitution per glucose unit.

Determination of the methoxyl group
See Apparatus and Procedure in Ethoxyl and Methoxyl Group Determination and determine the content of methoxyl group (-OCH3).

Calculation

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

A - (B x 0.93 x 31 / 75)

where
A = the total % of -OCH3 groups determined
B = the % of -OCH2CHOHCH3 determined in the Method of Assay for Hydroxypropoxyl group content
0.93 = an average obtained by determing, on a large number of samples, the propylene produced from the reaction of hydriodic acid with hydroxypropoxyl groups during the Method of Assay for metoxyl groups (-OCH3).

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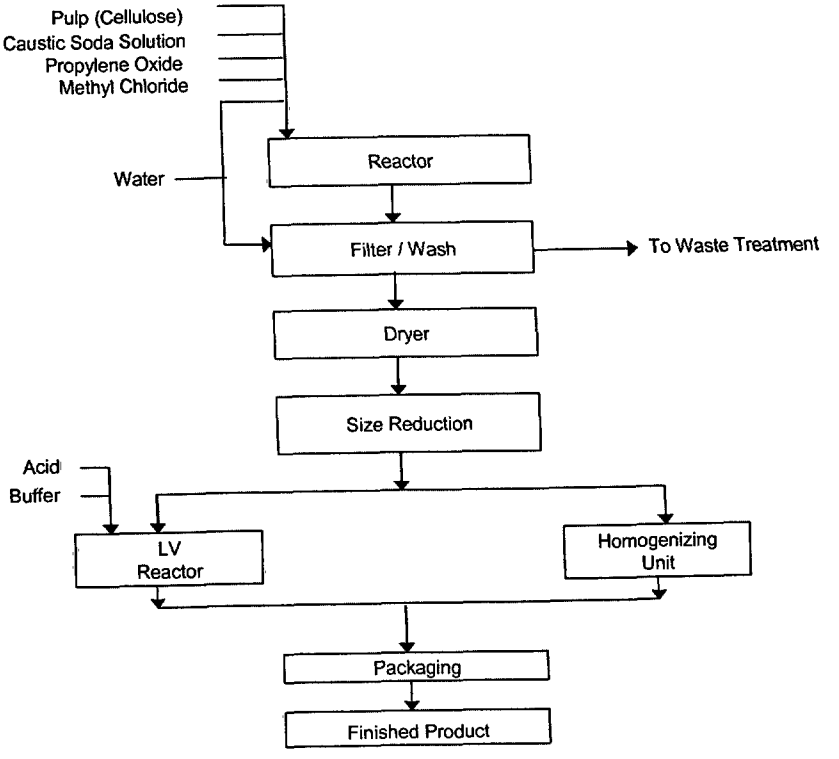
B

Appendix B

Appendix B: Process Flow Diagram

METHOCEL* Cellulose Ethers Process Flow Diagram



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C

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.

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.

D

Appendix D

Table 1. The upper limits of HPMC in food . The technical effect that controls the upper limit is established by undesirable viscosity, mouth feel, texture and off flavor of HPMC.

Food Category	Upper limit
Candies, soft chews 21 CFR § 170.3(n)(6, 25, 38)	(low viscosity) Food grades – 10.00% - upper limit (high viscosity) food grades – 8.00% - upper limit
Snacks, Pasta 21 CFR § 170.3(n)(23, 37)	(low viscosity) Food grades – 10.00% - upper limit (high viscosity) food grades – 8.00% - upper limit
Beverages 21 CFR § 170.3(n)(2, 3, 7, 31, 35)	(low viscosity) Food grades – 5.00% - upper limit (high viscosity) food grades – 2.00% - upper limit
Batters, Breader, Films, other Coatings, Seasonings 21 CFR § 170.3(n)(26)	(low viscosity) Food grades – 10.00% - upper limit (high viscosity) food grades – 10.00% - upper limit
Meat, Seafood, Poultry 21 CFR § 170.3(n)(13, 15, 17, 18, 29, 34)	(low viscosity) Food grades – 5.00% - upper limit (high viscosity) food grades – 5.00% - upper limit
Bakery, Baked Desserts, Baked Snacks 21 CFR § 170.3(n)(1)	(low viscosity) Food grades – 8.00% - upper limit (high viscosity) food grades – 6.00% - upper limit
Ice Cream, Sherbert, Frozen Desserts 21 CFR § 170.3(n)(10, 20, 21, 22)	(low viscosity) Food grades – 6.00% - upper limit (high viscosity) food grades – 6.00% - upper limit
Dairy, Cheese Products, Dairy and Non-Dairy Toppings 21 CFR § 170.3(n)(5, 10, 20)	(low viscosity) Food grades – 6.00% - upper limit (high viscosity) food grades – 6.00% - upper limit
Dips, Soups, Spreads - 21 CFR § 170.3(n)(24,36, 39, 40)	(low viscosity) Food grades - 8.00% - upper limit (high viscosity) food grades – 6.00% - upper limit

Food Category	Upper limit
Breakfast Cereals – 21 CFR § 170.3(n)(4)	(low viscosity) Food grades – 10.00% - upper limit (high viscosity) food grades – 10.00% - upper limit
Confections and Frostings 21 CFR § 170.3(n)(9)	(low viscosity) Food grades – 8.00% - upper limit (high viscosity) food grades – 6.00% - upper limit
Egg Products 21 CFR § 170.3(n)(11)	(low viscosity) Food grades – 8.00% - upper limit (high viscosity) food grades – 6.00% - upper limit
Jams and Jellies 21 CFR § 170.3(n)(27, 28)	(low viscosity) Food grades – 6.00% - upper limit (high viscosity) food grades – 6.00% - upper limit
Nuts and Nut Products 21 CFR § 170.3(n)(32)	(low viscosity) Food grades - 5.00% - upper limit (high viscosity) food grades – 5.00% - upper limit
Plant Protein Products 21 CFR § 170.3(n)(33)	(low viscosity) Food grades – 8.00% - upper limit (high viscosity) food grades – 8.00% - upper limit
Sugar Substitutes 21 CFR § 170.3(n)(42)	(low viscosity) Food grades - 3.00% - upper limit (high viscosity) food grades – 3.00% - upper limit

E

Appendix E

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

Table # in USDA Table Set 10	Product	Mean Quantity Consumed per Individual (grams)	Proposed Upper Limit (%) based on Table 1	Estimated Market Share (%)	HPMC(g/day)
Table 9.1. Grain products	Yeast, breads, and roll i.e. white breads with fiber added	50	8%	4 2%	0.17
	Cereals and pasta/Ready-to-eat-cereals i.e. breakfast cereals	16	10%	4 2%	0.07
	Cereals and pasta/Rice i.e rice mixes	23	10%	4.2%	0.10
	Cereals and pasta/Pasta i.e. fiber added pasta	18	10%	4.2%	0.08
	Quick breads, pancakes,french toast i.e tortillas, french toast	19	8%	4.2%	0.06
	Cakes, cookies, pastries, pies i.e. doughnuts, pound cake, pie filling, granola bars	38	8%	4.2%	0.13
	Crackers, popcorn, pretzels ,corn chips i.e fiber enhance corn chips	12	8%	4.2%	0.04
	Mixtures mainly grain i.e. pizza, frozen meals that are mainly grain/pasta	109	8%	14.0%	1.22
Table 9 2 Vegetables	White potatoes - Fried i.e. french fries, hash browns; potato chips	24	8%	4.2%	0.08
	Tomatoes i.e. ketchup, salsa	28	6%	10.0%	0.17
	Other vegetables i.e.vegetable soups, relishes	45	6%	7.0%	0.19
Table 9.3. Fruits	Other fruits, mixtures, and juice i.e. fruit desserts, fruit salads with dressing	96	8%	14.0%	1.08
	Citrus juices	60	5%	4.2%	0.13
	Noncitrus juices and nectars	27	5%	4.2%	0.06
Table 9.4. Milk and milk products	Yogurt	8	6%	4.2%	0.02
	Milk desserts i.e. ice cream, milk shakes	27	6%	7.0%	0.11
	Cheese i.e. cheese spreads; processed cheese slices	16	6%	4.2%	0.04
Table 9 5. Meat, poultry, and fish	Frankfurters, sausages, luncheon meats i.e. frankfurters	21	5%	4.2%	0.04
	Fish and shellfish ie. fis sticks and fish balls	10	5%	4.2%	0.02
	Mixtures mainly meat, poultry, fish i.e. frozen dinners, canned pasta	99	5%	14.0%	0.69
Table 9.6. Eggs;	Eggs i.e. omelettes, egg white substitute	18	8%	7.0%	0.10
legumes; nuts and seeds, fats and oils; sugars and sweets:	Legumes i.e. veggie burgers, meat substitutes	25	8%	7 0%	0.14
	Nuts and seeds i.e. peanut butter	4	5%	7.0%	0.01
	Table fats i.e margerine/butter replacements	4	8%	7.0%	0.02
	Salad Dressings i.e mayonnaise, salad dressings	8	8%	7 0%	0.04
	Sugars i.e sugar substitutes	3	3%	7.0%	0.01
	Candy ie. candy bars, fruit roll ups	7	10%	7.0%	0 05
Table 9 7 Beverages	Coffee i.e lattes, coffee mixes	259	5%	0 5%	0.06
	Tea i.e. tea mixes, chai teas	133	5%	0.5%	0 03
	Fruit drinks and ades - Regular ie. drink mixes, Koolaid	79	5%	4 2%	0.17
	Fruit drinks and ades - Low calorie	15	5%	7.0%	0.05
	Carbonated soft drinks - Regular	253	2%	4.2%	0.21
	Carbonated soft drinks - Low calorie	78	2%	7.0%	0.11
		HPMC EDI (Estimated Daily Intake) =			5.50

F

Appendix F

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[57] 56 Fed. Reg. 55454. Monday October 28, 1991. Indirect Additives: Adjuvants, Production Aids, and Sanitizers.

[58] 56 Fed. Reg. 55454 (Oct. 28, 1991).

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G

Appendix G

Jurisdiction:	Regulatory citation or Agency	Description of the citation:
United States - FDA	21 CFR § 172.874 21 CFR § 175.105 21 CFR § 175.300 21 CFR § 177.1960	21 CFR § 172.874 – Hydroxypropyl Methylcellulose. 21 CFR § 175.105 – Indirect Food Additives: Adhesives and Components of Coatings. 21 CFR § 175.300 – Indirect Food Additives: Adhesives and Components of Coatings; Resinous Coatings. 21 CFR § 177.1960 – Indirect Food Additives: Polymers.
United States - USDA	USDA – FSIS Directive 7120.1, Amendment 3, Safe and Suitable Ingredients used in the Production of Meat and Poultry Products, Attachment 1.	Seasoning mixtures added to sauces and gravies produced under FDA jurisdiction that will be used in meat and poultry products. Amount used is to be sufficient for purpose. Thickener in meat and poultry pot pie fillings, sauces, soups and gravies. Amount not to exceed 1 percent of the product formulation.

Jurisdiction:	Regulatory citation or Agency	Description of the citation:
CANADA:	Food and Drugs Regulations, Division 16: Food Additives, Table IV: Food Additives That May Be Used As Emulsifying, Gelling, Stabilizing and Thickening agents.	Item H.2, **Hydroxypropyl Methylcellulose**. Permitted in or upon (1) French dressing; (naming the flavour) Milk; Mustard pickles; Relishes; (naming the flavour) Skim milk; (naming the flavour) Partly skimmed milk; (naming the flavour); Skim milk with added milk solids; (naming the flavour) Partly skimmed milk with added milk solids; Salad dressing; and (2) Unstandardized foods, at a maximum level of use per Good Manufacturing Practices.
EUROPEAN UNION:	**European Parliament and Council Directive 95/2/EC of 20 February 1995 on food additives other than colours and sweeteners** *Official Journal L 061 , 18/03/1995 P. 0001 – 0040* ANNEX I FOOD ADDITIVES GENERALLY PERMITTED FOR USE IN FOODSTUFFS NOT REFERRED TO IN ARTICLE 2 (3)	**HPMC** is listed as an approved direct food additive.
SLOVENIA:	The valid legal act about the "Quality of Additives for Food" (SFRJ Nr 39/38 and 22/90)	**HPMC** is allowed for use in food as an agent for emulsification and stabilization.
POLAND:	The Polish Hygiene Institute (which is authorized by the Ministry of Health)	Confirmation that **HPMC** is allowed for use in foods. Certificates for the final product must be issued by the Hygiene Institute.
HUNGARY:	Hungarian Chamber of Commerce, Ministry of Agriculture	Confirmation that **HPMC** is allowed for use in foods.
CZECH REPUBLIC:	Czech Chamber of Commerce, Ministry of Health	Confirmation that **HPMC** is allowed for use in foods.

Jurisdiction:	Regulatory citation or Agency	Description of the citation:
JAPAN:	Japanese Standard of Food Additives (1994)	**Hydroxypropyl Methylcellulose (HPMC) (E, F, and K-type METHOCEL products)** is approved for limited use as a food additive in Japan. The Dow Chemical Company made a submission for HPMC to be registered and allowed as a food additive for making capsules and as a coating for nutritious application. The MHLW approval was published June 26, 2003, in The Official Gazette No. 3636.
SINGAPORE:	The Sale of Food Act (Chapter 283) (1990)	**Hydroxypropyl Methylcellulose** is considered approved under the "Permitted Emulsifiers and Permitted Stabilizers" category. The Act does not establish a limit on the use level. It does note that the Additive's purpose should be to aid in the formation or maintenance of a uniform dispersion of two or more immiscible substances.
MALAYSIA:	Laws of Malaysia: Food Act and Regulation	**Hydroxypropyl Methylcellulose** is considered approved under the "Permitted Food Conditioner: Stabilizers, thickeners, modified starches and gelling agents" category. The Act does not establish a limit on the use level nor does it describe the use category in more detail.
AUSTRALIA:	Australia New Zealand Food Authority "Food Standards Code"	**HPMC** is listed as a permitted food additive, when used in accordance with Good Manufacturing Practice.
NEW ZEALAND:	Australia New Zealand Food Authority "Food Standards Code"	**HPMC** is listed as a permitted food additive, when used in accordance with Good Manufacturing Practice.
HONG KONG:	Food Additive Regulations	**HPMC** is listed as an approved food additive.
TAIWAN:	Food Additive Regulations	**HPMC** is permitted for use in foods.
INDIA:	Food Additive Regulations	**HPMC** is approved for use in non-dairy toppings up to 2%.
ARGENTINA	Argentina "Codigo Alimentario, Chapter 1398, Section 93	**HPMC** is approved as a food additive.

H

Appendix H

Conclusion of the GRAS Panel Review of

Hydroxypropyl Mehthylcelluose

Based on my review of the scientific evidence, hydroxypropyl methylcellulose (HPMC) described in the GRAS Notification is generally recognized as safe (GRAS) for the conditions of the stated intended uses in food. It is my understanding that the class of HPMC products described in the GRAS Notification are to be used for a variety of functional uses, including as a source of dietary fiber. I further understand that the HPMC products added to food will comply with appropriate food grade specifications consistent with those described in the GRAS Notification.

Herbert Blumenthal, Ph.D.

Conclusion of the GRAS Panel Review of

Hydroxypropyl Mehthylcelluose

Based on my review of the scientific evidence, hydroxypropyl methylcellulose (HPMC) described in the GRAS Notification is generally recognized as safe (GRAS) for the conditions of the stated intended uses in food. It is my understanding that the class of HPMC products described in the GRAS Notification are to be used for a variety of functional uses, including as a source of dietary fiber. I further understand that the HPMC products added to food will comply with appropriate food grade specifications consistent with those described in the GRAS Notification.

26 December 2005

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

Conclusion of the GRAS Panel Review of

Hydroxypropyl Mehthylcelluose

Based on my review of the scientific evidence, hydroxypropyl methylcellulose (HPMC) described in the GRAS Notification is generally recognized as safe (GRAS) for the conditions of the stated intended uses in food. It is my understanding that the class of HPMC products described in the GRAS Notification are to be used for a variety of functional uses, including as a source of dietary fiber. I further understand that the HPMC products added to food will comply with appropriate food grade specifications consistent with those described in the GRAS Notification.

Michael W. Pariza, Ph.D.
Professor, Department of Food Microbiology & Toxicology
Director, Food Research Institute
University of Wisconsin–Madison
Madison, Wisconsin

SUBMISSION END

000086

Hendrickson, Carrie

From: Hill, Devon W. [Hill@khlaw.com]
Sent: Thursday, April 06, 2006 9:44 AM
To: Hendrickson, Carrie
Cc: Drozen, Melvin S.; Hill, Devon W.; Fallon, Eileen; Mathews, Robert A.
Subject: Withdrawal of Dow's GRAS Notification for HPMC
Attachments: Hendrickson 4-6-06.pdf

AM

Please see the attached. <<Hendrickson 4-6-06.pdf>>

APR 06 2006

Devon Wm. Hill
Partner
tel: 202.434.4279 | fax: 202.434.4646 | hill@khlaw.com
1001 G Street, N.W., Suite 500 West | Washington, D.C. 20001

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April 6, 2006

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Via Electronic Mail

Carrie A. Hendrickson, Ph.D.
Center for Food Safety and Applied Nutrition
Division of Biotechnology and
GRAS Notice Review, HFS-255
Food and Drug Administration
Room 2039
College Park, Maryland 20740

Re: GRAS Notice No. GRN 000190; Our File No. (b)(4)

Dear Dr. Hendrickson:

This will follow up on our recent telephone discussions. On behalf of The Dow Chemical Company, this will confirm that we are withdrawing the above-referenced notice without prejudice and with the opportunity to resubmit the notice in the future.

Thank you for your attention to this matter.

Very truly yours,

(b)(6)

Melvin S. Drozen

(b)(6)

Devon Wm. Hill

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OFFICE OF
FOOD ADDITIVE SAFETY

April 6, 2006

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Center for Food Safety and Applied Nutrition
Division of Biotechnology and
GRAS Notice Review, HFS-255
Food and Drug Administration
Room 2039
College Park, Maryland 20740

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Very truly yours,

(b)(6)

Melvin S. Drozen

(b)(6)

Devon Wm. Hill

Computer Technology Services, Inc.

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000097-000098

Reference List for Industry Submission, GRN 000190

Pages	*Author*	*Title*	*Publish Date*	*Publisher*	*BIB_Info*
000044 - 000045	NA	Hydroxypropyl Methylcellulose	NA	Food Chemicals Codex	NA
000046 - 000049	NA	Hypromellose	NA	Current USP - NF Monograph	NA
000050 - 000052	Committee on National Formulary under the Supervision of the Council, the authority of the American Pharmaceutical Association	Hydroxypropyl Methylcellulose	September 1, 1965	National Formulary XII	Twelfth Edition

NA- Not applicable