Safety assessment of hydroxypropyl methylcellulose as a food ingredient

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Abstract

Hydroxypropyl methyl cellulose (HPMC; CAS No. 9004-65-3) is an odorless and tasteless, white to slightly off-white, fibrous or granular, free-flowing powder that is a synthetic modification of the natural polymer, cellulose. It is used in the food industry as a multipurpose food ingredient. HPMC is approved by FDA as both a direct and an indirect food additive, and is approved for use as a food additive by the EU. The JECFA has evaluated the food uses of HPMC and established an acceptable daily intake (ADI) of ‘not specified’ for such uses. Based on the no-observed-adverse-effect level (NOAEL) of 5000 mg/kg body weight/day from a 90-day feeding study in rats, a tolerable intake for ingestion of HPMC by humans of 5 mg/kg body weight/day is posited and, as such, is more than 100-fold greater than the estimated current consumption of 0.047 mg/kg body weight/day.

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Keywords: Hydroxypropyl methylcellulose; Burdock; Toxicity; Food additive; GRAS

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Abbreviations: CAS, Chemical abstracts Service; CIR, Cosmetic Ingredient Review; CFR, Code of Federal Regulations; CoE, Council of Europe; CTFA, Cosmetic Toiletries and Fragrance Association; EC, European Community; EU, European Union; FCC, Food Chemicals Codex; FDA, United States Food and Drug Administration; GRAS, Generally Recognized As Safe; JECFA, Joint FAO/WHO Expert Committee on Food Additives and Contaminants; LSRO/FASEB, Life Sciences Research Office/Federation of Associated Societies of Experimental Biology; NAS, National Academy of Sciences; NOAEL, no-observed-adverse-effect level; SCF, Scientific Committee for Food; SCOGS, Select Committee On GRAS Substances; USDA, United States Department of Agriculture.

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1. Introduction

Hydroxypropyl methylcellulose (HPMC; CAS No. 9004-65-3) is used in the food industry as an emulsifier, film former, protective colloid, stabilizer, suspending agent, or thickener. HPMC is approved for food uses by the FDA (21 CFR 172.874) and the EU (EC, 1995); its safety in food use has been affirmed by the JECFA (JECFA, 2004). This review evaluates the safety-in-use of HPMC as a food ingredient.

1.1. Historical perspective

The historical record in the literature is not entirely clear on when HPMC was first introduced into food or any other commercial use. However, references point to a US patent on its preparation having been issued in 1960 to the Dow Chemical Company (Budavari et al., 1999), and also to safety data supported by Dow that date from the 1950s (Hodge et al., 1950; Knight et al., 1952). Thus, it may reasonably be inferred that large-scale commercial use of HPMC began in the 1960s and 1970s.

1.2. Description, natural occurrence and sources

Hydroxypropyl methylcellulose (Fig. 1) is an odorless and tasteless, white to slightly off-white, fibrous or granular, free-flowing powder that is a synthetic modification of the natural polymer, cellulose. Specifically, it is a modification of alkali cellulose, which is produced when purified wood pulp is treated with 18% sodium hydroxide solution. Methyl and hydroxypropyl ether groups are introduced into the molecule by reacting the alkali cellulose with methyl chloride and propylene oxide, respectively. The degree of substitution (DS) of commercial HPMC with these methoxy and hydroxypropoxy groups will vary depending on the commercial use and properties desired. These added groups confer on the molecule its unique properties of being cold-water soluble, while at the same time exhibiting reversible gelation when heated and recooled (BeMiller and Whistler, 1996; Burdock, 1997; Kibbe, 2000; Reilly, 2000). Additional descriptive characteristics and synonyms of HPMC are provided in Table 1.

1.3. Specifications

Specifications of HPMC from the Food Chemicals Codex (2003), JECFA (2006) and USP (2003) are presented in Table 2. HPMC is a polymer whose physical properties and molecular weight will vary depending on the DS with hydroxypropoxy and methoxy groups. JECFA (2006) has defined this molecular variation as follows (Fig. 2).

1.4. Uses of HPMC

HPMC finds use in the food, drug, and the dietary supplement industries. These uses are described in further detail below.

1.4.1. Uses as a food ingredient

The physical/chemical properties of HPMC described above make these materials useful in the food industry as stabilizers of emulsions and foams, as a replacement for fat and as a non-caloric bulking agent in foods, as a barrier to oil and in moisture retention, and as a binder. HPMC imparts little or no flavor to food (BeMiller and Whistler, 1996). The FDA- and EU-approved food uses of HPMC are provided in Table 3.

Fig. 1. Hydroxypropyl methylcellulose chemical structure.

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1 Additional uses of HPMC were the subject of a GRAS Notification (No. 000213, March 27, 2007) to which the US FDA had “no objection”. http://www.cfsan.fda.gov/~rdb/opa-g213.html (site visited 27 May 07).
Table 1

General description of hydroxypropyl methylcellulose

| Synonyms | Carbohydrate gum; cellulose hydroxypropyl methyl ether; cellulose, 2-hydroxypropyl methyl ether (9CI); hydroxypropyl methylcellulose; hydroxypropyl methylcellulose 1828; hydroxypropylmethylcellulosum; hypromellose; isopto alkaline; isopto frin; isopto plain; isopto tears; Lactel; Methocel E, F, K; Methocel E, F, J, K; Methocel HG; methylcellulose, propylene glycol ether of; methyl hydroxypropyl cellulose; methylhydroxycellulosum; propylene glycol ether of methylcellulose |
| CAS No. | 9004-65-3 |
| EU No. | E464 |
| INS No. | 464 |
| NAS No. | 0534 |
| Functional use | Processing aid, surface-finishing agent, texturizer, stabilizer or thickener, emulsifier or emulsifier salt, anticaking agent or free-flow agent drying agent, humectant |
| Chemical formula | Variable |
| Molecular weight | Variable |

CAS = Chemical Abstracts Service; EU = European Union; INS = International Numbering System and NAS = National Academy of Sciences.

Table 2

Hydroxypropyl methylcellulose specifications

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>White to off-white, fibrous powder or as granules</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Arsenic</td>
<td>NR</td>
<td>Not more than 3 mg/kg</td>
<td>NR</td>
</tr>
<tr>
<td>Assay for hydroxypropoxyl groups</td>
<td>3.0% min, 12.0% max</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Assay for methoxyl groups</td>
<td>19.0% min, 30.0% max</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Heavy metals (as Pb)</td>
<td>Not more than 10 mg/kg</td>
<td>Not more than 10 mg/kg</td>
<td>0.001%</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>Not more than 5.0%</td>
<td>Not more than 10% (105°C to constant weight)</td>
<td>Not more than 5.0%</td>
</tr>
<tr>
<td>pH</td>
<td>NR</td>
<td>Not less than 5 and not more than 8 (1 in 100 solution)</td>
<td>NR</td>
</tr>
<tr>
<td>Residue on ignition</td>
<td>Not more than 1.5% for products with viscosities of 50 cP or above, and not more than 3% for products with viscosities below 50 cP</td>
<td>Not more than 1.5% for products with viscosities of 50 cP or above, and not more than 3% for products with viscosities below 50 cP</td>
<td>Not more than 1.5% for hypromellose having labeled viscosities of greater than 50 cP, not more than 3% for products with viscosities below 50 cP</td>
</tr>
<tr>
<td>Solubility</td>
<td>Soluble in water and in certain organic solvent systems</td>
<td>Swelling in water, producing a clear to opalescent, viscous colloidal solution; insoluble in ethanol</td>
<td>NR</td>
</tr>
<tr>
<td>Viscosity</td>
<td>Not less than 80.0% and not more than 120.0% of that stated on the label for viscosity types of 100 cP or less, and not less than 75.0% and not more than 140.0% of that stated on the label for viscosity types higher than 100 cP</td>
<td>NR</td>
<td>Not less than 80.0% and not more than 120.0% on that stated on the label for viscosity types of 100 cP or less, and not less than 75.0% and not more than 140.0% of that stated on the label for viscosity types higher than 100 cP</td>
</tr>
</tbody>
</table>

FCC = Food Chemicals Codex; JECFA = Joint FAO/WHO Expert Committee on Food Additives; NR = not reported and USP = United States Pharmacopeia.

\[[\text{C}_{6}\text{H}_{7}\text{O}_{2}(\text{OH})_x(\text{OCH}_3)_y(\text{OCH}_2\text{CHOHCH}_3)_z]_n\], where

\[
z = 0.07 - 0.34
\]

\[
y = 1.12 - 2.03
\]

\[
x = 3(z + y); (z + y) = \text{degree of substitution}
\]

\[n = \text{number of repeating units in the polymer}
\]

Molecular weight of the polymer will vary with the value of ‘n’, ranging from approximately 13,000 when \(n = 70\), to approximately 200,000 when \(n \approx 1000\).

Fig. 2. Molecular variation of HPMC.
1.4.2. Uses in other categories

HPMC is used in the drug industry and is considered a 'pharmaceutical necessity' (Reilly, 2000). It finds use as a protective colloid by serving as a dispersing and thickening agent, as well as in ophthalmic solutions by providing the demulcent action and viscous properties essential for contact-lens use and in artificial-tear formulations (NLM, 2004; Murray, 2004a,b). The nonpyrogenic, viscoelastic properties of HPMC have also found use in ophthalmic surgery during procedures on the anterior segment of the eye, allowing for "more efficient manipulation with less trauma to the corneal endothelium and other ocular tissues" (Liesegang, 1993; Olin, 1995). In drug tablet formulations, HPMC is used for film-coating of tablets and as an extended-release tablet matrix (Kibbe, 2000). It is approved by the FDA for use as an "inactive ingredient" (21 CFR 210.3) in numerous oral, ophthalmic, and even topical nasal drug product preparations. HPMC has also been evaluated in humans as an alternative to gelatin as a source for two-piece hard capsules (Honkanen et al., 2001), including by the USDA as a potential organic source of these capsules for packaging some herbal dietary supplements (AMS/USDA, 2004). HPMC is also widely used in the cosmetics industry, primarily in hair shampoo, eye makeup, and skin care preparations, at concentrations ranging typically from 0.1% to 5% in product (CIR, 1986).

1.5. Regulatory history

The LSRO/FASEB included HPMC as one of several cellulose derivatives that it evaluated in a Select Committee On GRAS Substances (SCOGS) report (SCOGS, 1974) at the request of FDA, while noting that HPMC, itself, was not GRAS-listed. The Select Committee concluded that, "There is no evidence in the available information on [HPMC] 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" (SCOGS, 1974). HPMC, as part of the larger group of 'modified celluloses' has also been evaluated by the JECFA on numerous occasions, the most recent being in 1989 (JECFA, 1967, 1974, 1990, 2004). At this most recent meeting, the Committee reiterated its earlier assessment that modified celluloses "have a low toxicity" and assigned an ADI of "not specified". JECFA defines such a conclusion to mean that, "on the basis of the available data

<table>
<thead>
<tr>
<th>Agency</th>
<th>Comments</th>
<th>Permitted functionality</th>
<th>Use limits</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA</td>
<td>21 CFR 172.874 Food additives permitted for direct addition to food for human consumption. Subpart I – multipurpose additives</td>
<td>Multipurpose</td>
<td>May be used in food, except in standardized foods which do not provide for such use if: (a) The additive complies with the definition and specifications prescribed in the National Formulary, 12th edition. (b) It is used or intended for use as an emulsifier, film former, protective colloid, stabilizer, suspending agent or thickener, in accordance with good manufacture practice. (c) To insure safe use of the additive, the container of the additive... is subject to certain labeling requirements described in this section)</td>
<td>21CFR§172.874†††</td>
</tr>
<tr>
<td>FDA</td>
<td>21 CFR 175.105 Indirect food additives: adhesives and components of coatings. Subpart B – substances for use only as components of adhesives</td>
<td>Adhesive</td>
<td>Defined in regulation</td>
<td>21CFR§175.105††††</td>
</tr>
<tr>
<td>FDA</td>
<td>21 CFR 175.300 Indirect food additives: adhesives and components of coatings. Subpart C – substances for use as components of coatings</td>
<td>Resinous and polymeric coatings</td>
<td>Defined in regulation</td>
<td></td>
</tr>
<tr>
<td>EU</td>
<td>E464</td>
<td>Emulsifier, stabilizer, thickener, and gelling agent</td>
<td></td>
<td>FSA (UK) (2004)</td>
</tr>
<tr>
<td>NAS</td>
<td>534</td>
<td>Thickening agent; emulsifier; stabilizer</td>
<td>ADI: not specified; applies to the entire class of modified celluloses</td>
<td>Clydesdale (1997) JECFA (2004)</td>
</tr>
<tr>
<td>JECFA/INS</td>
<td>464</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


†††† US Code of Federal Regulations (CFR), Title 21, Section 175.105.
†† US Code of Federal Regulations (CFR), Title 21, Section 175.300.

Tables 3

Regulatory status of hydroxypropyl methylcellulose

<table>
<thead>
<tr>
<th>Agency</th>
<th>Comments</th>
<th>Permitted functionality</th>
<th>Use limits</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA</td>
<td>21 CFR 172.874 Food additives permitted for direct addition to food for human consumption. Subpart I – multipurpose additives</td>
<td>Multipurpose</td>
<td>May be used in food, except in standardized foods which do not provide for such use if: (a) The additive complies with the definition and specifications prescribed in the National Formulary, 12th edition. (b) It is used or intended for use as an emulsifier, film former, protective colloid, stabilizer, suspending agent or thickener, in accordance with good manufacture practice. (c) To insure safe use of the additive, the container of the additive... is subject to certain labeling requirements described in this section)</td>
<td>21CFR§172.874†††</td>
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<td>FDA</td>
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<td>Adhesive</td>
<td>Defined in regulation</td>
<td>21CFR§175.105††††</td>
</tr>
<tr>
<td>FDA</td>
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<td>Resinous and polymeric coatings</td>
<td>Defined in regulation</td>
<td></td>
</tr>
<tr>
<td>EU</td>
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<td>Emulsifier, stabilizer, thickener, and gelling agent</td>
<td></td>
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</tr>
<tr>
<td>NAS</td>
<td>534</td>
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<td>Clydesdale (1997) JECFA (2004)</td>
</tr>
<tr>
<td>JECFA/INS</td>
<td>464</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


† US Code of Federal Regulations (CFR), Title 21, Section 172.874.
†† US Code of Federal Regulations (CFR), Title 21, Section 175.105.
††† US Code of Federal Regulations (CFR), Title 21, Section 175.300.

2 US code of federal regulations (CFR), Title 21, Section 210.3.
(chemical, biochemical, toxicological, and other), the total daily 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 the Committee, represent a hazard to health. For that reason the establishment of an ADI expressed in numerical form is not deemed necessary (JECFA, 1990).

The approval of HPMC in the EU reflects the published opinions of the SCF (1994), wherein this Committee concurs with the above-noted opinions of JECFA that an ADI of “not specified” is appropriate for the group of five modified celluloses, including HPMC (E 464), that are approved for use as emulsifiers, stabilizers, thickeners, and gelling agents (EC, 1995). BIBRA has also published a profile of the available toxicity data on HPMC (BIBRA, 1989). The CIR Expert Panel of CTFA has evaluated the safety of cosmetic uses of HPMC and concluded them to be safe (CIR, 1986).

1.6. Consumption

Per capita estimate of intake is based on “disappearance data” from periodic surveys of ingredient manufacturers of the volume of ingredients produced during the survey year. The method is easy to use because it divides the total annual production by the population in the survey year and the number of days per year. The assumption is that there is a finite amount of substance available and the general population ingests it as an added food ingredient regardless of source at the retail level.

The primary sources of data for per capita estimates are the surveys conducted by the national academy of sciences (NAS) under contract to the FDA (NAS, 1989). The last survey, conducted in 1987, was based on voluntary reporting by manufacturers. Some considerations are necessary in the use of these survey data: (1) it is generally held that the amount reported is a fraction of the actual volume, because not all producers participate; and (2) distribution of consumption may be uneven, because not all persons eat all foods each day in each category in which the substance may be added and, conversely, some consumers may seek out the substance.

In order to compensate for these variables, the FDA assumes: (1) only 60% of the actual value was reported and (2) only 10% of the US population (243.9 million in 1987) consumes 100% of the calculated amount (NAS, 1989). Based on these variables and the annual poundage “disappearance” reported by the producers to the NAS of 33,600 lb for the year 1987 (NAS, 1989), the calculated individual consumption of HPMC is 2.85 mg/day or 0.047 mg/kg/day (for an average individual weighing 60 kg).

It is not clear how this estimate of dietary exposure would compare to HPMC exposures that result from pharmaceutical uses of HPMC, such as in tablets and capsules, as means for estimating these types of exposures are not available.

2. Biological data

2.1. Absorption, metabolism and excretion

The fate of ultra-low viscosity 14C-HPMC was investigated in rats following single- and repeated-dose oral administration (Gorzinski et al., 1986). One group of Sprague–Dawley rats (3/sex) was administered a single 500 mg/kg body weight gavage dose of the HPMC test article and then monitored for 72 h in glass metabolism chambers. Urine, feces, and expired CO2 were collected; blood was sampled via indwelling catheters. A second group of rats (also 3/sex) received five daily gavage doses of 500 mg/kg HPMC; these animals were housed in the metabolism chambers throughout the dosing interval and for 24 h after the last dose. Greater than 99% of the administered radioactivity was recovered in the feces and approximately 1% in the urine of rats following a single gavage dose of HPMC; recoveries following five consecutive daily doses were very similar. Plasma elimination half-life following a single dose of HPMC was 2.3 h in the males and 2.0 h in the females. The authors conclude that ultra-low viscosity HPMC is only minimally absorbed following oral administration, being excreted almost exclusively in the feces (Gorzinski et al., 1986); therefore, plasma elimination half-life is more likely a product of HPMC and metabolites, rather than HPMC per se.

2.2. Biochemical/pharmacological effects

HPMC was one of a number of non-digestible polysaccharides that were tested for their effects on the distal colon and resident microflora in rats, as well as for their in vitro fermentability (Wyatt et al., 1988). Male Wistar rats (5/test group) received for five days a basal diet that contained, as one constituent, sucrose at 300 g/kg diet and then received for 12 days a test diet in which HPMC replaced 100 g sucrose/kg of the basal diet (equivalent to a dose of 10 g HPMC/kg of body weight (FDA, 1993)). Animals were sacrificed following the feeding interval and the caecum, colon, and their contents analyzed. The authors conclude that caecal and colonic enlargement are due to a hypertrophic – as opposed to hyperplastic – response of the tissues to increases in bulk contents and that it is unlikely that short-chain fatty acids or any other microbial metabolites stimulate this response. In addition, HPMC was poorly fermented under in vitro assay conditions (Wyatt et al., 1988).

Johnson and co-workers (1988) have investigated the putative proliferation of gastrointestinal mucosal cells, as well as altered mucosal morphology and physiological activity, following prolonged consumption of viscous polysaccharide gums, including HPMC. Male Wistar rats (10/dose group) were fed for 14 days on a diet containing 10% HPMC (10 g/100 g diet, equivalent to 10 g HPMC/kg of body weight (FDA, 1993)) versus a fiber-free basal diet in control animals. Levels of plasma enteroglucagon
EG) – a generic name for a group of peptides homologous to pancreatic glucagon, but secreted by specialized cells in the distal gastrointestinal mucosa – were measured, as were ileal crypt cell production rate, crypt length, and small intestinal length. The authors concluded that viscous non-fermentable polysaccharide gums, such as HPMC, stimulate the release of EG and mucosal cell proliferation by slowing nutrient absorption (Johnson et al., 1988).

HPMC has been evaluated by numerous investigators for its ability to impact – positively and/or negatively – the absorption of other chemical entities across biological membranes, while remaining, *itself*, only minimally absorbed. These investigations have primarily focused on the general impact of HPMC on gastrointestinal absorption in mammalian systems of drugs and/or nutrients (Reppas et al., 1991; Zimmer et al., 1993; Slovin and Robinson, 1997). For example, Reppas and colleagues (Reppas and Dressman, 1992; Reppas et al., 1993, 1999) have conducted a number of investigations into the impact of the viscosity of HPMC on gastrointestinal absorption of glucose, in both dogs and humans. They conclude that HPMC can retard glucose absorption, thereby blunting postprandial blood glucose concentrations, and thus, may be useful as adjunct therapy in the treatment of diabetes; however, the effect was seen in humans at doses of 10 g/person (Reppas et al., 1993), approximately 3000 times greater than current consumption.

HPMC has also been evaluated more specifically – within the broad realm of drug absorption – in regards to its potential and efficacy as film-coating for tablet formulations (Said and Al Shora, 1981), in controlled-release tablet matrices (Davis et al., 1993; Kabanda et al., 1994, 1996; Yu et al., 1998; Velasco et al., 1999; Qiu et al., 2003; Vorapann et al., 2003), in hard capsule formulations (Meshali et al., 1989; Ojantakanen et al., 1993; Honkanen et al., 2002, 2004), as a transdermal drug delivery matrix (Fullerton et al., 1988; Verma and Patel, 1996; Verma and Lyrer, 2000), and as an agent to enhance drug adhesion to nasal (Zhou and Donovan, 1996), oral (Smart, 1993; Miyazaki et al., 2000), and gastrointestinal mucosal membranes (Chary et al., 1999).

HPMC has been investigated for its potential to lower blood cholesterol levels, putatively via a mechanism of increasing intraluminal viscosity in the gastrointestinal tract (Dressman et al., 1993; Schmidt et al., 1996; Swidan et al., 1996; Reppas et al., 1998; Carr et al., 2003). Reported findings suggest that it may have efficacy in this regard. Follow-up studies have been aimed at elucidating whether the administered dosage form of HPMC has an impact on this apparent efficacy – results suggest that it can (Swidan et al., 1996). In addition, there is the question of whether the presence of HPMC in the gastrointestinal tract can alter absorption of other drugs that a patient may be taking. Results suggest that it can alter absorption, primarily for compounds with absorption profiles that are dependant on gastric emptying, such as those that are highly water-soluble and reach peak plasma concentrations relatively quickly (Reppas et al., 1998), although again, at very high doses (7.5–10 g/dog).

Shibamoto et al. (1997) explored the radioprotective effect to SCCVII tumors in C3H mice given 1% HPMC (orally) 30 or 120 min prior to exposure of 15 Gy irradiation. The authors concluded the radioprotective effect (as measured by tumor regrowth) was present in the group dosed 30 min prior to irradiation, but there was no protective effect if irradiation preceded dosing by 120 min.

### 2.3. Toxicological studies

As has already been discussed (Section 1.5), JECFA has evaluated HPMC and other ‘modified cellulosics’ on numerous occasions, most recently in 1989, at which time an ADI of “not specified” was established (JECFA, 1967, 1974, 1990, 2004b). Based on the totality of information available for the group of substances as a whole, the Committee concluded there is no evidence that modified cellulosics possess mutagenic or carcinogenic activity, nor that they behave as developmental and/or reproductive toxicants. Available data specific to HPMC and/or close structural analogs are discussed in further detail in the sections that follow.

#### 2.3.1. Acute toxicity studies

Acute oral and dermal toxicity studies with hydrophobically modified HPMC were conducted in rats (Obara et al., 1992b). HPMC containing approximately 1.1% C16–C18 alkoxyhydroxyl content was administered orally *via* gavage to Crj:CD (SD) rats (5/sex/dose) in single doses of 0, 300, 600, or 900 mg/kg body weight, after which the animals were monitored for 14 days. The dermal toxicity study employed the same dosing groups, with the dose applied to the shaved backs of the rabbits for 24 h under occlusion. One animal in the high dose oral group exhibited loose stools 30 min after dosing. Otherwise, there were no abnormalities and no deaths observed in any treatment group, oral or dermal.

Data from acute toxicity studies conducted in 1950 are provided in Table 4. No further details from these studies are available.

<table>
<thead>
<tr>
<th>Species</th>
<th>Route</th>
<th>LD50 (g/kg)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>IP</td>
<td>5</td>
<td>Hodge et al. (1950)</td>
</tr>
<tr>
<td>Mouse</td>
<td>IP</td>
<td>5</td>
<td>Hodge et al. (1950)</td>
</tr>
</tbody>
</table>

LD50 = the dose that produces 50% lethality in the test population and IP = intraperitoneal.
25% HPMC in the diet for 30 days (mg/kg body weight dose to animals not provided). Severe diarrhea was evident in the high-dose group only, with 9/20 animals dying. No other effects were remarkable at any dose. Rabbits (6/dose; sex not specified) were fed 0%, 10%, or 25% HPMC in the diet for 30 days (mg/kg dose to animals not provided). There was no mortality in response to treatment; high-dose animals maintained their body weight, while the 10% group gained a little weight (approximately 0.5 kg). All other parameters evaluated were normal. Two dogs were also administered HPMC orally for an indeterminate duration (report indicates 30 days in one place and 52 days in another), one at 25 g/day and the other at 50 g/day. The dog receiving the higher dose exhibited some diarrhea, weight loss, and a small decrease in red blood cell count. No other findings were remarkable (Hodge et al., 1950).

2.3.3. Irritation studies

HPMC, hydrophobically modified (HM-HPMC) with approximately 1.1% \( C_{16-18} \) alkoxyhydroxypropyl content, was evaluated for its potential to cause skin and eye irritation in rabbits (Obara et al., 1992a). An aqueous 3% w/v dispersion of the HM-HPMC test article was tested in female Japanese white rabbits for dermal and eye irritancy according to Draize test methods. For dermal irritancy, test article was applied to intact and abraded skin for 24 h under occlusion, followed by rinsing and observation for up to seven days. In the eye test, 0.1 mL of test article was placed in the retracted lower left eyelid and then the eyelid held shut for several seconds; the right eye served as the untreated control. Six of nine treated eyes were rinsed following treatment; the remaining three were not rinsed. HM-HPMC was categorized as a “mild irritant” in the dermal assay; it was considered a “marginal” irritant to un-rinsed eyes and “negative” for irritancy in rinsed eyes.

2.3.4. Sensitization studies

HPMC, hydrophobically modified (HM-HPMC) with approximately 1.1% \( C_{16-18} \) alkoxyhydroxypropyl content, was evaluated for its skin sensitization/phototoxic sensitization potential in guinea pigs (Obara et al., 1998). Female Hartley guinea pigs were tested with an aqueous 3% w/v dispersion of the HM-HPMC under a maximization test protocol for sensitization assessment; an ‘adjuvant and stripping method’ was employed for the phototoxic sensitization assessment. There were no reactions indicative of either sensitization or phototoxic sensitization observed under the conditions of either assay. The authors report that the HM-HPMC test article does not induce skin sensitization or photosensitization under the conditions of the assay.

2.3.5. Subchronic toxicity studies

A six-month repeated-dose dermal toxicity study with 30-day recovery was conducted in SD rats with hydrophobically modified HPMC (Obara et al., 1997). HM-HPMC containing approximately 1.1% \( C_{16-18} \) alkoxyhydroxypropyl content was applied daily as an aqueous paste to the shaved backs of the animals (25/sex/dose) at doses of 0, 20, 40, or 60 mg/kg body weight/day. Five animals of each sex from each dosing group were maintained for an additional 30 days to assess reversibility of any observed effects. Parameters evaluated included clinical signs, urinalysis, hematology, ophthalmology, and histopathology. The authors report that no toxic effects attributable to test article administration were found.

McCollister et al. (1973) conducted subchronic dietary feeding studies in rats and dogs with HPMC of varying viscosities. Sprague–Dawley rats (10/sex/dose) were administered HPMC in the diet at concentrations of 0%, 1%, 3%, or 10% for 90 days; beagle dogs (2/sex/dose) received dietary HPMC at concentrations of 0%, 2%, or 6%, also for 90 days (conversion of dietary concentrations to mg/kg body weight doses was not provided). Parameters assessed included mortality, body weights, food consumption, urinalysis, hematology, serum chemistry, organ weights, and gross and microscopic histopathology. Except for some evidence of decreased food consumption in the treated rats, there were no treatment-related adverse effects reported by the authors in either rats or dogs.

Subchronic dietary feeding studies were conducted by Schwetz et al. (1976) in rats and dogs with a low-viscosity HPMC. Sprague–Dawley rats (15/sex/dose) were administered HPMC test article in the diet at concentrations of 0%, 1%, or 5% for 91 days; beagle dogs (4/sex/dose) were exposed to the same diets and for the same duration as were the rats. Hematology, urinalysis, clinical chemistry, organ weights, and gross and microscopic pathology were the parameters assessed in both studies. There were no changes noted in any of the parameters evaluated that could be attributed to treatment with either 1% or 5% dietary HPMC. Though information on dietary consumption by the animals was not provided in the report, based on standard FDA assumptions (FDA, 1993), these top dietary concentrations would correspond roughly to NOAELs of 5000 mg/kg body weight/day and 1250 mg/kg/day in the rat and dog, respectively. In addition, information provided in the report does not allow for certainty, but given the date of its conduct, it is unlikely that this study would be fully compliant with FDA Redbook testing guidelines (FDA, 1982).

A subchronic oral toxicity study with low-viscosity HPMC was conducted in rats (Obara et al., 1999). Crl:CD (SD) IGS rats (5/sex/dose) were administered HPMC via gavage at doses of 0, 505, 1020, or 2100 mg/kg body weight/day for 91 days. Parameters evaluated included clinical signs, hematology, serum chemistry, ophthalmology, organ weights, and gross and microscopic histopathology. On the basis of depressed body weights in both males and females at the highest dose tested, a dose of 1020 mg/kg body weight/day of low-viscosity HPMC was reported to be the NOAEL in the rat. No other treatment-related effects were noted by the authors.

White albino rats were fed diets containing HPMC of two different viscosities at concentrations of 0%, 0.3%, 1.0%, 3.0%, 10.0% or 20.0% for approximately three
months (McCollister et al., 1961). The two test articles differed in their degree of substitution with methoxyl and hydroxypropoxyl groups, one (Methocel 70HG) containing 24–27% methoxyl groups and 3.0–5.5% hydroxypropoxyl groups, and the other (Methocel 90HG) containing 19–24% methoxyl groups and 4–12% hydroxypropoxyl groups. Animals (10/sex/dose) were housed two per cage and had free access to food and water. Food consumption, body weights, and clinical signs were monitored on study; at necropsy, blood hematocrit and gross and microscopic pathology was evaluated. Statistical analyses were deemed not necessary. Actual mg/kg body weight doses of HPMC ingested by the animals were not reported, but would correspond to approximately 20 g/kg body weight/day at the highest dietary concentration tested, based on standard FDA assumptions (FDA, 1993). There was some growth retardation noted in the treated animals, primarily at the higher doses and more prevalent in males than in females. There was some mortality observed among treated animals, primarily at higher doses, which was judged unrelated to treatment. The authors concluded that both test materials are “extremely low in chronic oral toxicity” (McCollister et al., 1961).

Wistar rats (10/sex/dose) were fed HPMC in the diet at 0%, 1%, 3%, 10%, or 30% for 121 days (McCollister and Oyen, 1954). Animals were housed five per cage and had free access to food and water. Food consumption, general appearance, body weights, and mortality were monitored. Actual mg/kg doses of HPMC ingested by the animals were not reported, but would correspond to approximately 30 g/kg body weight/day at the highest dietary concentration tested, based on standard FDA assumptions (FDA, 1993). Terminal hematology analyses were performed on five females each from the control and 10% dose groups. Terminal necropsy was performed on all surviving animals, at which time livers and kidneys were weighed, and these and other tissues were prepared for microscopic histopathology. Ten of twenty high-dose animals died prior to scheduled necropsy, apparently due to undernourishment, and marked growth retardation was evident in those animals in this group that did survive. Slight growth retardation was also evident in males of the 10% dose group. No other tissue-specific toxicity was observed in the high-dose or any other dose group. The authors concluded this variant of HPMC to be similar to other HPMC variants in exhibiting “extremely low… chronic oral toxicity” (McCollister and Oyen, 1954).

2.4. Chronic toxicity/carcinogenicity studies

Two-year feeding studies were conducted in rats (strain not identified) with HPMC (Hodge et al., 1950). Animals (50/sex/dose; 5/cage) received 0%, 1%, 5%, or 20% HPMC in the diet ad libitum (mg/kg dose to the animals was not estimated by the authors, but would roughly correspond to 10 g/kg body weight/day at the high dose based on standard FDA assumptions (FDA, 1993)). Treatment with HPMC did not adversely impact lifespan of the animals. High-dose animals, particularly males, exhibited a significant decrease in weight gain, as well as a decrease in the total erythrocytes and hemoglobin. Histopathology analysis of benign and neoplastic tissues was reported to be unremarkable, as were all other parameters evaluated. An additional chronic study in dogs was conducted. Animals (2/dose) received oral doses of 0, 0.1, 0.3, 1.0, or 3.0 g/kg/day for one year. There was no reported mortality in response to treatment and all parameters as described for the rat experiments were reported to be within normal limits (Hodge et al., 1950).

2.5. Teratogenicity/reproduction toxicity

An English abstract from one of a series of Japanese reports describe results of reproductive and developmental toxicity studies in Crj:CD (SD) rats with a new antineoplastic agent, Emitefur, wherein HPMC (1% solution) was the vehicle that was administered to control animals at 5 mL/kg (Ishizuka et al., 1994). There was no report of any adverse effects in this HPMC control group, though a group treated with water alone was not included to allow a basis for comparison.

A similar abstract describes studies by Ford et al. (1992) of the developmental toxicity of all-trans retinoic acid in Wistar rats, in which 0.5% HPMC was the vehicle for gavage administration and, therefore, was the sole treatment received by control animals. As in the abstract from Ishizuka et al. (1994) above, there was no indication of any adverse effects in the HPMC control group, though a group treated with water alone was not included to allow a basis for comparison.

2.6. Observations in humans

Knight et al. (1952) report on studies in 25 normal, healthy young adults (23 male, 2 female) that each received a total of three individual and increasing doses of HMPC ranging from 0.6 to 8.9 g, with at least one week between each dose. Subjects were instructed to avoid certain foods, and to keep a record of his/her bowel habits and any associated effects. Stool specimens were collected for three to four days after each dose at approximately 24-h intervals. Essentially all of the administered doses were eliminated in the feces within the first 96 h and the only notable effects recorded consisted of a mild laxative or constipating effect in several of the subjects (Knight et al., 1952).

JEFCFA (1990) comments that the laxative effects in humans of modified celluloses, including HPMC, is generally recognized and known to occur in some subjects at levels as low as 5 g/person/day. At higher doses, both diarrhea and constipation have been reported. The Committee recounts the recommendation of the US National Research Council that 30 g/day in total of dietary fiber – a general classification to which modified celluloses belong – be considered a safe upper intake level.
3. Discussion

HPMC is an odorless and tasteless, white to slightly off-white, fibrous or granular, free-flowing powder that is a synthetic modification of the natural polymer, cellulose. It is used in the food industry as a multipurpose food ingredient. HPMC is approved by FDA as both a direct and an indirect food additive, and is approved for use as a food additive by the EU. JECFA has evaluated the food uses of HPMC and established an ADI of ‘not specified’ for such uses.

HPMC has been shown generally to exhibit a very low order of toxicity in mammalian systems. Data show orally administered HPMC, and modified celluloses as a whole, to pass through the mammalian gastrointestinal tract largely unabsorbed and unchanged, behaving effectively as non-nutritive fiber. Rats have been exposed to HPMC of variable viscosity in dietary concentrations ranging up to 20–30% for durations of 90–120 days with little evidence of adverse effects other than growth retardation at the highest doses. Dogs exposed for 90 days to HPMC at 5% of their diet exhibited no adverse effects. Chronic data on HPMC, specifically, as well as on other modified celluloses, indicate that these materials do not possess mutagenic or carcinogenic potential, neither do they behave as developmental or reproductive toxicants. HPMC and modified celluloses have not been reported as irritants or sensitizers.

4. Conclusion

Comparing the NOAEL of 5000 mg/kg/day from a 90-day feeding study in rats (Schwetz et al., 1976) and an estimated consumption of 0.047 mg HPMC/kg body weight/day, a theoretical safety factor of >100,000 exists. These data indicate that at the current level of intake, HPMC does not pose a health risk to humans.

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References


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