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Final Report on the Safety Assessment of Hydroxyethylcellulose, Hydroxypropylcellulose, Methylcellulose, Hydroxypropyl Methylcellulose, and Cellulose Gum

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.

INTRODUCTION

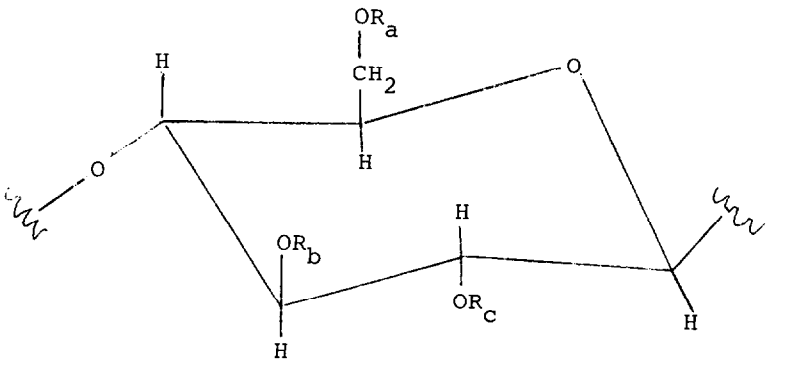
The literature on Methylcellulose, Hydroxypropyl Methylcellulose, and Cellulose Gum dating from 1920 to 1973 has been previously reviewed in a GRAS report and evaluation, and is only briefly summarized here.[1,2] A survey of the most recent literature, pertinent articles not included in the GRAS report and

evaluation, as well as the unpublished cosmetic industry data on these three celluloses have been included. Hydroxyethylcellulose and Hydroxypropylcellulose are reviewed in full.

CHEMICAL AND PHYSICAL PROPERTIES

General

Hydroxyethylcellulose (HEC), Hydroxypropylcellulose (HPC), Methylcellulose (MC), Hydroxypropyl Methylcellulose (HPMC), and Cellulose Gum (CG) are modified cellulose polymers with the general subunit structure:



For HEC:[3]	$R = (-CH_2-CH_2-O-)_nH$ $a + b + c = 1.5$ to 3	*n* may equal zero
For HPC:[4]	$R = (-C_3H_6-O-)_nH$ $a + b + c =$ usually 3	*n* may equal zero
For MC:[5]	$R = (-CH_3)$ or H $a + b + c = 1.62$ to 1.92	
For HPMC:[6]	$R = (-CH_3)$ or $(-C_3H_6-O-)_nH$ $a + b + c = 1.12$ to 2.03	*n* may equal zero
For CG:[7]	$R = (-CH_2-COONa)$ or H $a + b + c = 0.3$ to 1.2	

These cellulose ethers are derived from the reaction of the three free hydroxyl groups in the 2–, 3–, and 6– positions of the anhydroglucose unit of the cellulose molecule. The number of hydroxyl groups reacting and the nature of the substituent group largely determine the physical properties, particularly solubility, of the product. The viscosity of the final product is greatly affected by the molecular weight of the starting cellulose. All of these ethers are odorless, tasteless, and very stable chemically.[8]

Hydroxyethylcellulose

HEC is a white, odorless, tasteless powder that has a pH of 6.5–8.5 as a 1% aqueous solution.[9] It is soluble in hot and cold water, 70% soluble in alcohol, and generally insoluble in organic solvents, with the exception of dimethylsulfoxide.[3,10] The surface chemical properties of HEC have been studied in depth by Holly[11,12]; HEC was found to be weakly surface active. The reader is referred to Savage et al.[13] for a complete review of the chemistry of this ingredient. The physicochemical properties of HEC and the other cellulose derivatives are listed in Table 1.

HEC is prepared by reacting alkali cellulose with ethylene oxide in the presence of alcohol or acetone. The molar substitution, or MS, is the average number of moles of ethylene oxide that become attached to the anhydroglucose cellulose unit at either the hydroxyl groups in the chain or at previously reacted hydroxyl groups. The degree of substitution, or DS, is the average number of hydroxyl groups substituted per anhydroglucose unit.[10] HEC is commonly manufactured with an MS of 1.8 and 2.5; 2.5 gives optimum water solubility and strong resistance to enzymic attack.[10,14] However, the various grades range from an MS of 1.5 to 3.0. Solution viscosities vary greatly within each MS level.[10] The DS ranges from 1.5 to 3 (max = 3).[3] HEC is one of the more valuable cellulose derivatives because it is available in a treated form that produces rapid dispersion in aqueous solutions.[10] Other specific grades may contain additives to delay hydration, prevent lumping, and retard bacterial growth.[3]

HEC can be identified by close matching to a standard infrared spectrum with no indication of foreign materials.[15]

Being nonionic in character, HEC does not react with polyvalent cations, and in solution is generally unaffected by moderate shifts in pH. HEC is compatible with sodium chloride (0.5–26%), alum (2.0%), ammonium sulfate (10.0%), atropine sulfate, pilocarpine-hydrochloric acid, detreomycin, zinc sulfate, potassium iodide, and some anionic and amphoteric surfactants (12.5%) depending on specific concentrations.[10,16] Increased flocculating action on kaolin suspensions has been demonstrated by HEC graft copolymerized with acrylamide.[17] HEC has increased the dissolution rate of p-aminosalicylic acid tablets[18] and also accelerated the release rate of chlorpromazine, dioxopromethazine, oxytetracycline, and sulfathiazole from hydrogels.[19]

HEC is stable under the typical conditions of cosmetic use.[3]

Haugen et al.[14] studied the steady shear flow properties, rheological reproducibility, and stability of aqueous HEC dispersions over a period of 5 years. Dispersions of 1.5–3.5% HEC had shear-thinning flow properties. Each 0.5% increment in polymer concentration substantially increased apparent viscosity and non-Newtonian behavior. Over the 5-year storage period, apparent viscosity decreased with time, and behavior became more Newtonian within each dispersion concentration.

Solutions of HEC are susceptible to bacterial degradation and must be properly preserved for long-term stability.[20] Eros and Csordas[21] studied the effect of various preservatives and temperatures on the viscosity and stability of HEC solutions over a 3-month period. The solution preserved with methyl 4-hydroxybenzoate remained nearly unchanged, whereas those without preservatives had

TABLE 1. Physicochemical Properties

Property	Values for HEC	HPC	MC	HPMC	CG
Physical appearance	White, odorless, tasteless powder[3,9,15]	White, odorless, tasteless granular powder[4,15]	White to off-white, odorless, tasteless, fibrous powder[1,5]	White to off-white fibrous powder[1,6]	White to cream colored, odorless, tasteless, powder[1,7]
Formula weight per anhydroglucose unit	206 minimum[3]	223 minimum[4]	166.3–190.5[5]	177–279[6]	185–258[7]
pH of:					
1% aqueous solution	6.5–8.5[9]	6.0–8.0[15]	–	–	6.5–8.5[27,29]
2% aqueous solution	6.0–8.0[15]	5.0–8.5[4]	–	–	7.5[7]
5% aqueous solution	6.0–8.5[3]	–	–	–	–
Viscosity (Brookfield at 25°C, cps)					
1% solids	800–5000[3]	40–2500[4,20]	8[20]	–	69[20]; 1000–5000[7]
2% solids	25–6500[3]	75–6500[4]	10–8000[20]	10–8000[1]	10–50,000[1,7,20]
5% solids	75–400[3]	25–400[4]	400[20]	–	115,500[20]
10% solids	–	100–700[4]	–	–	–
Particle size	90% minimum through 40 mesh[3]	95 and 99% minimums 30 and 20 mesh, respectively[4]	–	–	–
Bulk density (g/ml)	–	0.5[4]	0.25–0.70[5]	0.25–0.70[6]	0.75[7]
Moisture (% maximum)	5.0[3,9,15]	5.0[4,15]	3.0, 5[27,29]	3.0, 5.0[15,29]	8.0, 10[27,29]
Ash (% maximum)	5.0[9]	0.5[4]	2.0, 1.5[27,29]	1.5–3.0[15,29]	–
Sodium chloride (% maximum)	–	–	1.0[5]	0.5[6]	–
Sodium					9.5 after drying[27]

Heavy metals (maximum)	–	40 ppm[27]	10 ppm[29]	10 ppm[29]	40 ppm[27,29]
Lead	–	10 ppm[27]	10 ppm[27]	10 ppm[27]	10 ppm[27]
Arsenic	–	3 ppm[27]	3 ppm[27,29]	3 ppm[27]	3 ppm[27]
Refractive index (2% aqueous, 20°C)	–	1.337[4]	1.336[5]	1.336[6]	–
Specific gravity					
1% aqueous	–	–	1.0112[5]	1.0112[6]	–
5% aqueous	–	–	1.0117[5]	1.0117[6]	–
10% aqueous	–	–	1.0245[5]	1.0245[6]	–
Solubility[a]					
Water	S[3,10]	S at <40°C; I at >40°C[20]	S (cold only)[1,20]	S (cold only)[20,25]	D,[27] S[20]
Alcohol	S (to 70%)[10]	S[15]	I[1]	–	I[1]
Organic solvents	S-Dimethylsulfoxide only[10]	S in polar solvents[20]	S–glacial acetic acid, and limited number[1,27]	S–most polar solvents[25]	I[1]
Surface activity (in water)					
Surface tension (dynes/cm)	64[10]	45[10]	–	50[10]	71[10]
Interfacial tension	Reduced[10]	Greatly reduced[10]	–	Reduced[10]	Unchanged[10]
Film properties					
Tensile strength (psi)	4000[10]	2000[10]	–	3000[10]	12,000[10]
Elongation at break	25%[10]	50%[10]	–	35%[10]	10%[10]
Flexibility (at 50% relative humidity [R.H.])	Good[10]	Excellent[10]	–	Good[10]	Poor[10]
Equilibrium moisture content (at 50% R.H.)	6%[10]	3%[10]	–	4%[10]	15%[10]
Blocking tendency (at 90% R.H.)	Some[10]	None[10]	–	Little[10]	Considerable[10]
Density of film	–	–	–	–	1.59 g/ml[7]
Minimum ignition temperature	420°C[28]	–	–	–	–

[a]S, soluble; I, insoluble; D, disperses.

significant decreases in viscosity related to time. The viscosity of all solutions decreased exponentially with temperature increase.

HEC has demonstrated synergistic viscosity when combined with an equal amount of an anionic cellulose derivative. The resultant viscosity has been almost double that expected. HEC (viscosity of 1800 cps) combined with CG (viscosity of 1500 cps) had an actual viscosity of 3200 cps when the expected viscosity was 1650 cps.[10]

Hydroxypropylcellulose

HPC is a white, hygroscopic, odorless, and tasteless granular powder. This nonionic polymer is soluble in water, below 40°C, alcohol, and most polar organic solvents.[20] A 2% aqueous solution has a pH of 5.0 to 8.5[4] (Table 1). The reader is referred to Desmarais[22] for a complete review of the chemistry of this ingredient.

HPC is prepared commercially by reacting cellulose with sodium hydroxide and propylene oxide under proprietary conditions. The DS is usually 3;[4] the MS is usually greater than 3.[20] Silicon dioxide (0.3%) may be added as an anticaking agent.[4]

HPC can be identified by close matching to a standard infrared spectrum with no indication of foreign materials.[15]

HPC is stable under typical cosmetic use conditions.[4] Solutions are generally stable in the pH range of 3–10. HPC is available in several viscosity types and is compatible with most common inorganic salts (at low salt concentration) and with most natural gums and synthetic water-soluble polymers. Viscosity increases rapidly with concentration. Aqueous solutions of HPC exhibit Newtonian behavior at low shear rates but become more thixotropic at high shear rates. HPC is very surface-active, has good film-forming properties, and forms films with excellent flexibility and heat-sealing properties.[20] It is particularly useful as an emulsifier and thickener in oil-in-water emulsions.[10,20]

Methylcellulose

MC is a white to off-white, odorless, tasteless, hygroscopic powder.[5] It is soluble in cold water, glacial acetic acid, and in a mixture of equal parts ethanol and chloroform, whereas it is insoluble in hot water, ethanol, ether, and chloroform.[20,23] (Table 1). The reader is referred to Savage et al.[13] and Greminger and Savage[24] for a complete review of the chemistry of this ingredient.

MC is prepared by reacting cellulose fibers (cotton linters or wood pulp) with caustic soda to produce alkali cellulose, which is then reacted with methyl chloride. The product is purified and ground. The extent of alklylation and polymer chain length are controlled in order to produce a derivative with specific characteristics. For cosmetic use, the DS ranges from 1.62 to 1.92.[5] This is within the DS range that has maximum water solubility.[20]

MC can be identified by close matching to a standard infrared spectrum with no indication of foreign materials.[23]

MC is stable under typical cosmetic use conditions.[5] Solutions of MC increase in viscosity on heating and eventually gel at 50–55°C. This gel point can be elevated by the addition of ethanol or propylene glycol, while most electro-

lytes, as well as sucrose, glycerol, and sorbitol, depress the gel point. MC solutions, being neutral and nonionic, are relatively stable over a pH range of 3–11 and are not affected by ordinary concentrations of electrolytes or other solutes.[20] The presence of inorganic salts does increase solution viscosity. Clear water-soluble films may be cast from aqueous or mixed solvent (methanol–water) solutions of MC.[20,25]

Hydroxypropyl Methylcellulose

HPMC is a white to off-white, fibrous, hygroscopic powder.[6,15] It is soluble in cold water and in most polar organic solvents[20,25] (Table 1). The reader is referred to Greminger and Savage[24] for a complete review of the chemistry of this ingredient.

HPMC is prepared by reacting cellulose fibers (cotton linters or wood pulp) with caustic soda, methyl chloride, and propylene oxide. This product is purified and ground. The extent of alkylation and polymer chain length are controlled in order to produce a derivative with specific characteristics. For cosmetic use, the DS ranges from 1.12 to 2.03,[6] with the number of methoxyl substitutions typically much larger than the number of hydroxypropyl substitutions.[10]

HPMC can be identified by close matching to a standard infrared spectrum with no indication of foreign materials.[23]

HPMC is stable under typical cosmetic use conditions.[6] Aqueous solutions are surface-active, form films upon drying, and exhibit thermogelling properties. Depending on the amounts and ratios of methyl and hydroxylpropyl groups, the gel point can be raised as high as 85–90°C in commercial products.[10,20,25]

Cellulose Gum

CG is a white to cream-colored, hygroscopic, odorless, and tasteless powder. Chemically, it is the sodium salt of carboxymethylcellulose (CMC). It is insoluble in alcohol, ether, and in most organic solvents, but disperses easily in water to form a viscous solution[23] (Table 1). The reader is referred to Savage et al.[13] and Batdorf[26] for a complete review of the chemistry of CG.

Because CMC is spontaneously converted to the sodium salt in alkaline solution, much of the literature makes no distinction between the two.[2] Therefore, pertinent information on CMC has been included in this report.

CG is manufactured by treating cellulose (cotton linters or wood pulp) with alkali followed by reaction with sodium monochloroacetate. The resulting product is then purified.[7] The reaction is controlled to give the desired DS degree of polymerization (DP) and uniformity of substitution, as this determines the properties of the finished product.[20] For cosmetic use, the DS ranges from 0.3 to 1.2.[7]

CG can be identified by close matching to the CTFA standard infrared spectrum with no indication of foreign materials.[23]

CG is stable under typical cosmetic use conditions.[7] It exhibits a reversible loss of viscosity on heating. Solutions are fairly stable between pH 5 and 11. CG is compatible with most other water-soluble gums and is generally unaffected by high concentrations of monovalent salts.[10,20] It forms clear films that are resistant to oils and most organic solvents.[20]

USE

Cosmetic Uses

The cellulose derivatives are used in a wide variety of cosmetics and toiletries as thickeners, suspending agents, film formers, stabilizers, emulsifiers, emollients, binders, or water-retention agents.[3-7,10] Generally, the majority of uses is in hair products, eye and facial makeups, and skin care preparations. The concentration of use can range up to 10%. However, the celluloses are most frequently used in concentrations of >0.1–1%[30] (Table 2).

The FDA cosmetic product formulation data presented in Table 2 are compiled through voluntary filing of such data in accordance with Title 21 part 720.4 (d) (1) of the Code of Federal Regulations (1979). Ingredients are listed in prescribed concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product; the actual concentration in such a case would be a fraction of that reported to the FDA. Since data are only submitted within the framework of preset concentration ranges, there is also the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a 2- to 10-fold error in the assumed ingredient concentration.[30]

The formulation data presented in Table 2 indicate that cosmetic products containing the cellulose derivatives may contact all external body surfaces and hair, as well as ocular and vaginal mucosae. HEC, MC, and CG also have the potential to contact the oral mucosae. These products may be used daily or occasionally over a period of up to several years. The frequency and length of application could result in continuous exposure.

HEC, HPC, and CG are approved for use in cosmetics in Japan.[31]

Hydroxyethylcellulose

In 1981, HEC was used in a total of 422 formulations, most of which were hair, hair coloring, eye makeup, and skin care preparations. Of these 422, 71% incorporated HEC at concentrations of >0.1–1%; 22% at concentrations of >1–5%; 6% at concentrations ≤0.1%; and less than 1% at concentrations >5–10%.[30]

Hydroxypropylcellulose

In 1981, HPC was used in a total of 82 formulations, most of which were fragrance and hair (noncoloring) preparations. Of these 82, 90% incorporated HPC at concentrations of >0.1–1; 9% at concentrations of >1–5%; and 1% at concentrations ≤0.1%.[30]

Methylcellulose

In 1981, MC was used in a total of 144 formulations, most of which were blushers, eye makeup, and skin care preparations. Of these 144, 53% were of unreported MC concentration; 17% at concentrations of >0.1–1%; 16% at concentrations of >1–5%; and 13% at concentrations ≤0.1%.[30]

TABLE 2. Product Formulation Data[30]

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)				
			Unreported concentration	>5–10	>1–5	>0.1–1	≤0.1
Hydroxyethylcellulose							
Bubble baths	475	3	–	–	–	3	–
Eyeliner	396	19	–	–	9	10	–
Eye shadow	2582	12	–	–	–	12	–
Mascara	397	54	–	–	7	43	4
Other eye makeup preparations	230	7	–	–	1	6	–
Colognes and toilet waters	1120	1	–	–	–	1	–
Perfumes	657	11	–	–	–	11	–
Hair conditioners	478	55	–	–	16	38	1
Hair straighteners	64	6	–	–	2	4	–
Permanent waves	474	10	–	–	1	9	–
Hair rinses (noncoloring)	158	7	–	–	3	3	1
Hair shampoos (noncoloring)	909	16	–	–	2	14	–
Wave sets	180	3	–	–	–	3	–
Other hair preparations (noncoloring)	177	4	–	–	2	2	–
Hair dyes and colors (all types requiring caution statement and patch test)	811	56	–	–	31	25	–
Hair rinses (coloring)	76	52	–	–	–	34	18
Hair bleaches	111	4	–	1	3	–	–
Other hair coloring preparations	49	1	–	–	1	–	–
Blushers (all types)	819	3	–	–	–	3	–
Face powders	555	1	–	–	–	1	–
Makeup foundations	740	10	–	–	–	10	–
Makeup bases	831	6	–	–	–	6	–
Other makeup preparations (not eye)	520	1	–	–	1	–	–
Nail creams and lotions	25	1	–	–	–	–	1
Dentifrices (aerosol, liquid, pastes, and powders)	42	1	–	–	–	1	–
Bath soaps and detergents	148	2	–	–	1	1	–
Deodorants (underarm)	239	2	–	–	–	2	–
Other personal cleanliness products	227	4	–	–	–	4	–
Aftershave lotions	282	2	–	–	–	1	1

TABLE 2. (Continued)

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)				
			Unreported concentration	>5–10	>1–5	>0.1–1	≤0.1
Shaving cream (aerosol, brushless, and lather)	114	1	–	–	–	1	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	7	–	–	4	3	–
Depilatories	32	6	–	–	2	4	–
Face, body, and hand skin care preparations (excluding shaving preparations)	832	12	–	–	3	8	1
Moisturizing skin care preparations	747	18	–	–	–	18	–
Paste masks (mud packs)	171	10	–	2	3	5	–
Skin lighteners	44	2	–	–	–	2	–
Skin fresheners	260	2	–	–	–	2	–
Wrinkle smoothers (removers)	38	1	–	–	–	1	–
Other skin care preparations	349	6	–	–	2	4	–
Suntan gels, creams, and liquids	164	3	–	–	–	3	–
1981 TOTALS		422	–	3	94	298	27
Hydroxypropylcellulose							
Bath oils, tablets, and salts	237	2	–	–	–	2	–
Bubble baths	475	1	–	–	–	1	–
Other bath preparations	132	3	–	–	–	3	–
Eyeliner	396	1	–	–	1	–	–
Colognes and toilet waters	1120	3	–	–	–	3	–
Perfumes	657	38	–	–	1	36	1
Other fragrance preparations	191	14	–	–	2	12	–
Hair conditioners	478	6	–	–	1	5	–
Hair rinses (noncoloring)	158	1	–	–	–	1	–
Hair shampoos (noncoloring)	909	2	–	–	2	–	–
Tonics, dressings, and other hair grooming aids	290	1	–	–	–	1	–
Wave sets	180	1	–	–	–	1	–
Other hair preparations (noncoloring)	177	1	–	–	–	1	–

Nail polish and enamel remover	41	2	–	–	–	2	–
Deodorants (underarm)	239	1	–	–	–	1	–
Aftershave lotions	282	1	–	–	–	1	–
Other shaving preparation products	29	1	–	–	–	1	–
Face, body, and hand skin care preparations (excluding shaving preparations)	832	1	–	–	–	1	–
Skin fresheners	260	1	–	–	–	1	–
Suntan gels, creams, and liquids	164	1	–	–	–	1	–
1981 TOTALS		82	–	–	7	74	1
Methylcellulose							
Bubble baths	475	1	–	–	–	1	–
Eyeliner	396	13	–	–	10	2	1
Eye shadow	2582	5	1	–	1	1	2
Eye makeup remover	81	2	–	–	2	–	–
Mascara	397	1	1	–	–	–	–
Other eye makeup preparations	230	1	–	–	1	–	–
Colognes and toilet waters	1120	4	4	–	–	–	–
Other fragrance preparations	191	1	1	–	–	–	–
Hair conditioners	478	1	–	–	–	1	–
Hair shampoos (noncoloring)	909	8	–	–	1	7	–
Wave sets	180	1	–	–	–	1	–
Hair dyes and colors (all types requiring caution statement and patch test)	811	1	–	–	1	–	–
Hair rinses (coloring)	76	4	–	–	–	–	4
Hair shampoos (coloring)	16	1	–	–	1	–	–
Blushers (all types)	819	59	55	–	–	–	4
Makeup foundations	740	1	1	–	–	–	–
Lipstick	3319	1	1	–	–	–	–
Rouges	211	1	1	–	–	–	–
Other makeup preparations (not eye)	530	4	–	–	1	–	3
Cuticle softeners	32	2	–	–	2	–	–
Deodorants (underarm)	239	1	–	–	–	1	–
Other personal cleanliness products	227	1	–	–	–	1	–
Aftershave lotions	282	4	2	–	–	–	2
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	6	1	–	1	3	1

TABLE 2. (Continued)

Product category	*Total no. of formulations in category*	*Total no. containing ingredient*	*No. of product formulations within each concentration range (%)*				
			Unreported concentration	*>5–10*	*>1–5*	*>0.1–1*	*≤0.1*
Face, body, and hand skin care preparations (excluding shaving preparations)	832	3	–	–	–	1	2
Moisturizing skin care preparations	747	6	2	–	–	4	–
Night skin care preparations	219	1	–	–	–	–	1
Paste masks (mud packs)	171	1	1	–	–	–	–
Wrinkle smoothers (removers)	38	1	–	–	–	1	–
Other skin care preparations	349	7	5	–	2	–	–
Other suntan preparations	28	1	–	–	–	1	–
1981 TOTALS		144	76	–	23	25	20
Hydroxypropl Methylcellulose							
Baby products	15	1	–	–	–	1	–
Bath oils, tablets, and salts	237	1	–	–	–	1	–
Bubble baths	475	8	–	–	–	8	–
Other bath preparations	132	4	2	–	1	1	–
Eyeliner	396	3	1	–	1	1	–
Eye shadow	2582	3	–	–	–	3	–
Mascara	397	6	–	–	2	3	1
Other eye makeup preparations	230	2	–	–	1	1	–
Hair conditioners	478	4	–	–	–	4	–
Hair rinses (noncoloring)	158	6	–	–	2	4	–
Hair shampoos (noncoloring)	909	87	–	–	22	64	1
Hair dyes and colors (all types requiring caution statement and patch test)	811	3	–	–	1	2	–
Hair shampoos (coloring)	16	2	–	–	–	2	–
Hair bleaches	111	11	–	2	7	2	–
Makeup preparations (not eye)	530	1	–	–	–	1	–
Cuticle softeners	32	2	–	–	2	–	–

Bath soaps and detergents	148	5	–	–	–	5	–
Deodorants (underarm)	239	9	–	–	3	6	–
Douches	26	1	–	–	–	1	–
Other personal cleanliness products	227	3	–	–	–	3	–
Aftershave lotions	282	1	–	–	–	–	1
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	10	–	–	2	5	3
Face, body, and hand skin care preparations (excluding shaving preparations)	832	2	–	–	–	1	1
Moisturizing skin care preparations	747	4	–	–	–	4	–
Night skin care preparations	219	2	–	–	–	2	–
Paste masks (mud packs)	171	9	–	1	6	2	–
Wrinkle smoothers (removers)	38	1	–	–	–	–	1
Other skin care preparations	349	4	–	–	3	1	–
Suntan gels, creams, and liquids	164	1	–	–	–	1	–
Other suntan preparations	28	1	–	–	–	1	–
1981 TOTALS		197	3	3	53	130	8
Cellulose Gum							
Bath oils, tablets, and salts	237	5	–	–	–	5	–
Eyeliner	396	43	16	–	–	20	7
Eye shadow	2582	61	6	–	5	29	21
Mascara	397	19	–	–	–	19	–
Other eye makeup preparations	230	16	–	–	–	13	3
Sachets	119	2	–	–	–	2	–
Other fragrance preparations	191	4	–	–	–	2	2
Hair conditioners	478	1	–	–	–	1	–
Hair shampoos (noncoloring)	909	3	–	–	–	3	–
Tonics, dressings, and other hair grooming aids	290	2	–	–	2	–	–
Wave sets	180	1	–	–	–	1	–
Hair dyes and colors (all types requiring caution statement and patch test)	811	1	–	–	1	–	–
Hair bleaches	111	1	–	–	1	–	–
Blushers (all types)	819	50	2	–	1	39	8
Face powders	555	1	–	–	1	–	–

TABLE 2. (Continued)

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)				
			Unreported concentration	>5–10	>1–5	>0.1–1	≤0.1
Makeup foundations	740	239	35	–	–	185	19
Lipstick	3319	2	1	–	–	–	1
Makeup bases	831	220	18	–	1	177	24
Rouges	211	6	–	–	–	6	–
Makeup fixatives	22	3	3	–	–	–	–
Other makeup preparations (not eye)	530	14	5	–	–	9	–
Cuticle softeners	32	1	–	–	1	–	–
Other manicuring preparations	50	1	–	–	–	1	–
Dentifrices (aerosol, liquid, pastes, and powders)	42	12	–	–	8	4	–
Bath soaps and detergents	148	1	–	–	–	–	1
Other personal cleaniness products	227	3	–	–	–	3	–
Aftershave lotions	282	2	–	–	–	1	1
Other shaving preparation products	29	1	–	–	–	1	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	18	–	–	2	11	5
Face, body, and hand skin care preparations (excluding shaving preparations)	832	26	–	–	1	17	8
Moisturizing skin care preparations	747	31	4	–	–	23	4
Night skin care preparations	219	1	–	–	–	1	–
Paste masks (mud packs)	171	9	–	–	–	9	–
Skin fresheners	260	1	–	–	–	1	–
Wrinkle smoothers (removers)	38	3	–	–	1	2	–
Other skin care preparations	349	5	–	–	–	3	2
Suntan gels, creams, and liquids	164	3	–	–	–	3	–
1981 TOTALS		812	90	–	25	591	106

Hydroxypropyl Methylcellulose

In 1981, HPMC was used in a total of 197 formulations, most of which were hair shampoos, eye makeup, and skin care preparations. Of these 197, 66% incorporated HPMC at concentrations of >0.1–1%; 27% at concentrations of >1–5%; 4% at concentrations ≤0.1%; and 2% at concentrations of >5–10%.[30]

Cellulose Gum

In 1981, CG was used in a total of 812 formulations, most of which were eye and skin makeup and skin care preparations. Of these 812, 11% incorporated CG at unreported concentrations; 73% at concentrations of >0.1–1%; 13% at concentrations ≤0.1%; and 3% at concentrations of >1–5%.[30]

Noncosmetic Use

Hydroxyethylcellulose

HEC has a myriad of uses in the industrial, medical, dental, veterinary, and diagnostic fields. It is used as a thickener and emulsifier in disinfectant solutions, antimicrobial pastes, pesticides, paints, and paint removers. HEC alone, and as a graft copolymer, is utilized as a flocculating agent in the treatment of waste waters. It is used for its film-forming effect in selective insecticides and in remedies for the treatment of spilled hazardous liquids.[32–40]

In the pharmaceutical industry, HEC is used extensively as a binder and adjuvant in tableting, as a thickener and stabilizer in artificial tears, medicated eye drops, and contact lens solutions. Additionally, HEC is found in contraceptives and other vaginal products and in compositions for the treatment of oral and nasal mucosal infections. It is also used as the vehicle or suspending agent for intravenous and intraperitoneal instillation of water-insoluble drugs and other compounds.[41–58]

In the medical field, HEC is the protective polymer for activated carbon in hemoperfusion and artificial kidney devices. It is the drag-reducing agent used to decrease the hemolysis rate during the mechanical pumping of blood in open-heart and other surgeries. HEC is used as a suspending agent for chemicals and in the treatment of phosphorus burns. It is used as an absorbent in surgical dressings, bandages, and sponge substitutes and is used in adhesives for surgical tapes to improve moisture permeability.[59–71]

In dentistry HEC is used in pastes and sponge substitutes to provide enamel protection and in film-forming compositions for the removal of nicotine tar from teeth. The veterinary field uses HEC as a thickening and film-forming agent in a composition for the prevention of bovine mastitis. HEC is also used as a viscosity controller, film-coating polymer, and suspending agent in various diagnostic techniques.[72–84]

HEC is listed as an indirect food additive for use as an adhesive component (with no limitations), polymeric coating used in producing, treating, packaging, transporting, or holding food, and in a water-insoluble form in cellophane sheets and films for food packaging (with no limitations).[85–88]

Hydroxypropylcellulose

HPC is used in the pharmaceutical industry as a tablet-coating agent, topical protectant, and ophthalmic vehicle. It is found in menstrual tampons and in medicated compositions applied to vaginal and nasal mucosae.[25,47,50,89-95]

HPC is also used as a binder in ceramics and glazes, in vaccum-formed containers and blow-molded bottles, and as a suspending agent in PVC polymerization.[25]

HPC is listed as a direct food additive (DFA) for use as an emulsifer, film former, protective colloid, stabilizer, suspending agent, or thickener in accordance with good manufacturing practices (GMPs). It is also approved as a binder and disintegrator in tablets or wafers containing dietary supplements of vitamins and/or minerals.[96] As an indirect food additive (IFA), HPC is used as a basic component of food contact surfaces.[87]

Methylcellulose and Hydroxypropyl Methylcellulose

MC and HPMC are used in the pharmaceutical industry as film formers and tablet-coating agents, bulking and suspending agents, surfactants, thickeners, stabilizers, and protective colloids. The FDA OTC (over-the-counter) drug review program concluded that MC was safe in the amounts usually taken orally (2 g/day) in antacid products but that insufficient data existed to prove its effectiveness.[97] Subsequently, no data were submitted during the 2-year probationary period, and MC is now classified as generally not safe or effective for antacid use.[98]

MC and HPMC are used in agricultural sprays, ceramics, cements, paints, textiles, and papers.[24] MC is also used as a veterinary laxative in daily to twice daily doses of 0.5–1.0 g for cats and 0.5–5.0 g for dogs.[99]

MC has been approved by FDA as a multiple-purpose GRAS (generally recognized as safe) food substance.[100] HPMC is approved as a DFA when used in accordance with GMPs.[101] Both of these ingredients are used in foods as emulsifiers, film formers, protective colloids, stabilizers, suspending agents, or thickener.[24,101] As IFAs, HPMC and MC are used as adhesive components and polymeric coatings in the production, treatment, packaging, transporting, and/or holding of food;[85,86,102] MC is also used in paper and paperboards as a defoaming agent.[103] MC was first used in foods in the United States in 1960.[1]

Cellulose Gum

CG is used in the pharmaceutical industry as a tablet excipient, suspending and viscosity increasing agent, bulk laxative, demulcent, dental adhesive, and as an absorption medium.[25,104,105] The FDA OTC drug review program concluded that CG was safe in the amounts usually taken orally (3 g/day) in antacid products but that insufficient data existed to prove its effectiveness.[97] Subsequently, no data were submitted during the 2-year probationary period, and CG is now classified as not safe or effective for antacid use.[98]

CG is used widely in textiles, paper, adhesives, insecticides, paints, ceramics, lithography, and detergents.[20] It is used in veterinary drugs as a suspending agent.[99]

CG has been approved by FDA as a multiple purpose GRAS food additive.[106,107] It functions as a stabilizer, protective colloid, bulking agent, and

water-retention agent.[20] CG is also approved as a secondary DFA for specific use in boiler water,[108] and as an IFA used in adhesives and polymeric coatings for the packaging and transporting of food.[85,86] CG was first used in foods in the United States in 1945.[1]

GENERAL BIOLOGY

Biochemical Effects

Okada and Fletcher[109] studied the inactivation by radiation of deoxyribonuclease I in aqueous solution with high concentrations of HEC. Inactivation of the enzyme depended on the concentrations of both HEC and the enzyme; however, it was not influenced by the viscosity of the system. Each increase of HEC resulted in an increase in the dose of radiation required to inactivate the enzyme.

The oral administration of 500 and 1000 mg/kg HPC did not influence the mobility of barium sulfate in the small intestine of mice, the formation of stress ulcers in rats, or the bile secretion in rats.[110]

The effects of MC on the absorption of nitrofurantoin administered orally to humans was studied. MC (5.0% solution) delayed the absorption and urinary excretion without altering the bioavailability of nitrofurantoin.[1,111] A similar delay in the intestinal absorption of sulfafurazole suspended in MC was noted in rats.[112] MC and CG did not exhibit an inhibitory effect on the intestinal absorption of acetaminophen in rats.[113]

Phenytoin and hexobarbital hydrophilized with MC demonstrated increased gastrointestinal bioavailability both in vitro (tests with treated plugs vs pure drug) and in vivo (study in human volunteers).[114,115] Oral absorption of acetohexamide and tolbutamide in rats was improved by using capsule formulations containing MC and HPMC.[116]

The ocular pharmacokinetics of pilocarpine-HCl in human eyes were studied using HPMC as a vehicle. The amount of pilocarpine-HCl absorbed increased with increasing concentrations of HPMC.[117]

Dietary fibers, including CG, were studied for their effects on the gastrointestinal absorption of cadmium. CG produced a slight decrease in the cadmium content of the tissues of rats following a single oral administration of the metal. However, a significant decrease in the cadmium content of the tissues was noted in rats fed continuously with a diet containing cadmium and CG. The inhibitory effects of the fibers on the gastrointestinal absorption of cadmium appear to be due to their intrinsic properties, particularly binding ability and viscosity.[118]

CG, as a dietary fiber at 5% in the diet, had no significant effect on the serum lipids and liver lipid metabolism and urinary ascorbic acid content in rats fed 0.03% polychlorinated biphenyls (PCBs).[119]

Weanling rats fed a basal diet containing 4% amaranth (food Red No. 2) and CG had less growth retardation than those receiving a basal diet with amaranth alone. CG had a moderate protective effect against the toxicity of amaranth.[120]

Aspirin and salicylic acid suspended in 1% wt/vol dispersions of CG were absorbed in significantly greater amounts from the gastrointestinal tract of rabbits than when administered alone. The effect of viscosity on the gastric emptying

rate apparently was responsible for the variation in bioavailability of aspirin from the suspensions.[121]

A 1% solution of CMC in saline administered intraperitoneally (ip) (0.2 ml/10 g) to mice 5 hours before an ip injection of doxorubicin enhanced the hepatotoxicity of this antibiotic. Lethality increased to 80% compared to 15% in mice administered doxorubicin alone. The heart, liver, kidneys, and small bowel were examined microscopically and the incidence and severity of hepatic damage were increased in mice receiving both doxorubicin and CMC. A significant reduction in hepatic glutathione was noted in mice receiving CMC and doxorubicin plus CMC in comparison to the controls and mice receiving doxorubicin alone.[122] CMC also mildly decreased hepatic glutathione concentrations in hamsters.[123]

A 1% (wt/vol) solution of CMC added to fetal calf serum ($\leq$5%) stimulated a dissociation of cellular aggregates and an extensive outgrowth of neurites in mouse neuroblastoma cells. Neurite formation increased proportionally with the concentration of CMC during the first 24 h of incubation, plateauing at 1% CMC. In rat pheochromocytoma cells, the addition of CMC in the absence of nerve growth factor (NGF) produced no significant neurite outgrowth; however, cells pretreated with CMC for 1 day responded to NGF with a more rapid rate of neurite outgrowth than control cells not pretreated with CMC. The extent of outgrowth in this case was the same. Neither dialysis of CMC nor batch treatment of culture medium with CMC prior to incubation enhanced neurite outgrowth. Incubation on CMC-coated dishes also did not enhance outgrowth. The effects of CMC were attributed to possible increased cell–substratum adhesion or to changes in cell membrane permeability.[124]

Tissue Effects

The efficacy and toxicity of intraocularly administered MC were studied in rabbits. The three-part study consisted of an in-vitro corneal endothelial perfusion test, an intraocular pressure test following anterior chamber injection, and an endothelial abrasion test. A 0.4% MC solution in saline was nontoxic to the corneal endothelium. Injection of the same into the anterior chamber moderately increased intraocular pressure, although this was stabilized in the normal range by 24 h. The MC solution provided only minimal endothelial protection from polymethylmethacrylate intraocular lens surfaces.[125]

Physiological Effects

HEC of approximate molecular weight 30,000 was injected intravenously (iv) in mice in doses of 600 to 1200 mg/kg in a study of vascular permeability effects. The mice also received an iv injection of Evans blue immediately after the administration of HEC; bluing of the ears was used as the indicator of increased vascular permeability. HEC failed to cause bluing of the ears in any of the test animals and therefore was not associated with an increase in vascular permeability.[126]

Surgical procedures were carried out on 7 mongrel dogs involving the insertion of a hot film anemometer probe into the left renal artery adjacent to the wall

of the descending aorta. This allowed measurements of aortic wall flow disturbance distal to a controlled partial occlusion. HEC was administered through a femoral vein catheter as a 0.5% solution in 0.9% saline to test its effects as a vascular drag-reducing agent. Administration continued up to a concentration of 60 ppm by weight in the bloodstream. HEC was relatively inefficient in reducing vascular wall disturbances due to its lack of efficiency in imparting viscoelastic character to the blood.[127] However, other experimenters have reported that adequate levels of viscoelasticity may exist in HEC at concentrations of 500–700 ppm.[128]

Two groups of rabbits were used in electroretinograph studies conducted under identical circumstances except for different coating agents on the corneal electrode surface consisting of ophthalmic artificial tear solutions containing 1.6 and 0.2% HEC, respectively. Five humans were also similarly studied. Retinal responses obtained with the 0.2% HEC tear solution increased up to 81% in comparison to the values recorded with the 1.6% solution. The difference in electrical conductivity of the two solutions was correlated with differences in electroretinographic amplitudes and was also time dependent.[129]

Aqueous solutions of HPC at concentrations of 0.5 and 1.0% did not cause local anesthesia in the cornea of the 6 rabbits tested.[110]

The physiological effects of repeated ip injections of MC have been studied in mice[130–133] and in rats.[134–136] Stang and Boggs[130] injected mice with 0.5 ml of a 2.5% MC solution three times weekly for 4 weeks. They found that MC produced a partially compensated hemolytic anemia, thrombocytopenia, neutrophilia, increased splenic hematopoiesis, and hepatic hematopoiesis. These changes were attributed to reticuloendothelial hyperplasia caused by macrophage ingestion of MC. Changes in the blood cells became fairly steady after 2 weeks of MC injection and were not affected by splenectomy. Pfrimmer et al.[131] also studied the effects on mice after similar injections of MC and found that MC was still visible in macrophages of the spleen and liver up to 40 weeks later. Twice weekly injections of 2.5% MC solution into rats for a 15-week period produced splenomegaly with anemia, hyperplasia of the bone marrow elements, reticulocytosis, leukopenia, varying thrombocytopenia, ascites, and infiltration of the spleen, liver, and kidneys with storage-cell macrophages.[134] Renal injury was present in rats administered 10 × 50 mg ip injections of MC over a 30-day period.[135] Splenectomy in the rat prior to administration of MC prevented the development of hematological abnormalities.[134,135]

Absorption, Distribution, Metabolism, and Excretion

The absorption, distribution, metabolism, and excretion of orally ingested cellulose and its derivatives have been studied extensively. The published literature prior to 1974 indicates that cellulose derivatives pass unchanged through the gastrointestinal tract following oral administration in rats, dogs, and man. Rabbits apparently digest about 50% of the ingested amount of CG, although this has been attributed to bacterial action present only in herbivorous animals.[1,2]

Kitagawa et al.[137] studied the fate of ^{14}C-HPC (labeled in the hydroxypropyl group) orally administered to rats. The ^{14}C-HPC and nonradioactive HPC were suspended in 15% gum arabic solution and administered by stomach tube to

male and female rats at a dose of 1.3 g/kg. Radioactivity was measured in the urine, feces, bile, tissues, and gastrointestinal tract. The radioactivity was almost completely excreted in the feces, which, at 96 h, accounted for 97.3 and 96.8% of the radioactivity ingested by the males and females, respectively. A combined total of 99.9 and 98.3% of the radioactivity was excreted in the urine and feces (at 96 h) of the males and females, respectively. The radioactivity in the bile and tissues was very low; the highest level was found in the liver, although only trace amounts remained at 72 h. Radioactivity in the gastrointestinal tract decreased to 1.5% after 48 h and was less than 0.05% after 72 h. Urine metabolite radioactivity was insufficient for complete analysis. It was concluded that HPC is poorly absorbed from the gastrointestinal tract in the rat.

Another metabolism study was conducted in which ^{14}C-HPC was orally administered to 2 male and 2 female rats at doses of 250 mg/kg and 1000 mg/kg. Radioactivity was measured in the expired air, urine, feces, blood, liver, kidneys, and gastrointestinal tract. No radioactivity was detectable in the expired air or blood. The urine contained about 3.2% of the total radioactivity at 24 h. The feces contained 96–100.5% of the radioactivity at 96 h, with the greatest amount being excreted between 12 and 48 h. The liver, kidneys, and gastrointestinal tract contained 0–0.25% of the administered doses.[138]

A distribution study was conducted in rats with ^{14}C-CG. Five male rats received 0.4 g ^{14}C-CG in 18 ml of water by stomach tube; a similar dose of unlabeled CG was administered to another 5 rats as controls. Urine was collected for 44 h, at which time the animals were killed and samples were taken of the stomach, small and large intestine, liver, and kidneys. Almost all of the radioactivity was found in the large and small intestine; activities in the urine, kidneys, and liver were comparable to controls.[139]

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

An acute oral LD_{50} test was conducted on a 50% (wt/vol) solution of HEC in corn oil. Doses of 6834, 10250, 15380, and 23070 mg/kg were administered by oral intubation to groups of 4 rats. After a 14-day observation period, all rats were necropsied. No deaths or gross pathological changes were noted. Reactions included hypoactivity and ruffed fur in all groups and diarrhea for 2 days in rats of the highest dose group[140] (Table 3).

In another test for oral toxicity, a single dose of HEC in a 10.9% aqueous dispersion was administered to 10 male albino rats, giving an effective dose of 8.7 g/kg body weight. This was the largest single dose possible due to the limitation of the viscosity of HEC water dispersions. No effects on appetite and growth, no deaths, and no lesions were noted during the 14-day observation period[141] (Table 3).

Low, middle, and high viscosity HPC solutions (aqueous) had oral LD_{50}s > 5 g/kg in mice and rats.[142] No mortalities resulted when rats were administered HPC in gum arabic solution in as large a dose as possible, considering their gas-

tric capacity. The acute oral LD_{50} was defined as >15 g/kg HPC.[143] Similarly, no deaths occurred when HPC was administered as a 10% aqueous solution to rats at an oral dose of 10.2 g/kg[144] (Table 3).

A conditioning polish remover containing 0.7% HPC had an acute oral LD_{50} of 10.1 ml/kg (or 8.2 g/kg) in rats[145] (Table 3).

HPMC administered to rats in single oral doses of up to 4 g/kg produced no toxic effects[1,146] (Table 3).

CMC administered to rats, rabbits, and guinea pigs in single oral doses of 5 g/kg produced no toxic effects.[1] A cosmetic eye makeup product containing 0.605% CMC had an oral LD_{50} > 50 g/kg[147] (Table 3).

CG administered to rats, rabbits, and guinea pigs in single oral doses of 3 g/kg produced no toxic effects.[1,148] Acute oral LD_{50}s of CG were approximately 27 g/kg in rats and 16 g/kg in guinea pigs.[1,149,150] The LD_{50}s of various cosmetic products containing 0.3–3.0% CG are reported in Table 3.

Intraperitoneal

No deaths or toxicity resulted from single ip injections of 2.5 g/kg HPC in male mice (10) and male and female rats (10 of each sex).[142]

A 5% MC solution injected ip into mice (18 groups of 10 males) gave an LD_0 of 147 ml/kg and an ED_0 of 1.0 ml/kg.[1]

HPMC injected ip into 138 mice had an approximate LD_{50} of 5 g/kg.[1]

Usmanov et al.[156] reported that CMC was essentially nontoxic when injected ip into mice. CMC particles were found in the pulmonary reticuloendothelial cells 48 h after 6 rats were injected ip with 1 ml of a 1.6% CG solution.[1]

Intravenous

No deaths or other toxic effects resulted when HPC was injected iv at a dose of 0.5 and 0.25 g/kg in mice (10 males) and rats (10 of each sex), respectively.[142]

Rabbits injected iv with 10 mg/kg MC developed leukopenia; however, injections of 10–100 ml/kg of a 1% MC solution had no effect on blood pressure or respiration.[1] Transient hyperlipemia and small atherosclerotic lesions of the aorta were noted in 3 of 8 surviving rabbits injected iv with 25 ml of a 1.2% (wt/vol) aqueous solution of MC or 50 ml (divided into three injections) of a 0.5% (wt/vol) saline solution of MC.[157]

Hueper[136,158,159] reported that iv injections of MC administered to dogs and rabbits caused hematological alterations and retention and accumulation of MC in the liver, spleen, lymph nodes, kidney, and vascular walls. He also found that single iv doses of CMC caused only mild transitory shifts in the cellular elements of the blood of the treated dogs.[160]

Usmanov et al.[156] reported that the iv toxicity of CMC in mice was strongly related to its degree of substitution, degree of polymerization, and distribution range. Increasing the degree of substitution increased acute toxicity, although not proportionally.

Subcutaneous

Usmanov et al.[156] reported that CMC was essentially nontoxic to mice when injected subcutaneously.

TABLE 3. Acute Oral Toxicity

Ingredient	*Animal*	*No. of animals*	*LD_{50} (g/kg)*	*Comments*	*Reference*
HEC 50% solution in corn oil	Rat	4 per group	>23.07	Ruffed fur and hypoactivity; some diarrhea at high dose level	140
HEC 10.9% in aqueous solution	Rat	10	>8.7	No toxic effects	141
HPC in aqueous solution	Rat	60	>5	Light ataxia and inactivity on first day only; no deaths	142
	Mouse	30	>5	Light ataxia and inactivity on first day only; no deaths	142
HPC in gum arabic solution	Rat	30	>15	No deaths	143
HPC 10% in aqueous solution	Rat	25	>10.2	No deaths; some lassitude on first day	144
HPC 0.7% in conditioning polish remover	Rat	40	8.2	–	145
HPMC	Rat	11	>4	No toxic effects	1
HPMC 5% in aqueous solution	Rat	15	>1	No toxic effects	146
CMC in olive oil and aqueous gum arabic	Rat	Unspecified	>5	No toxic effects	1
	Rabbit	Unspecified	>5	No toxic effects	1
	Guinea pig	Unspecified	>5	No toxic effects	1

CMC 0.605% in eye product	Rat	10	>50	Two deaths due to mechanical obstruction of intestine at high dose; no toxic effect in others	147
CG 3% in aqueous solution	Rat	Unspecified	>3	No toxic effects	1
	Rabbit	Unspecified	>3	No toxic effects	1
	Guinea pig	Unspecified	>3	No toxic effects	1
CG 2.5% in aqueous solution	Rat	12	>3	Ruffed fur and hypoactivity; no deaths	148
CG	Rat	Unspecified	27	LD_{100} = 40 g/kg; no effect level of 20 g/kg	1
CG 1 g in 2.5 ml olive oil	Rat	40	27	–	149
CG	Guinea pig	Unspecified	16	LD_0 = 10 g/kg	1
CG 1 g in 2.5 ml olive oil	Guinea pig	30	16	–	150
CG 3.0% in wrinkle-smoothing cream	Rat	5	>15	No deaths, no toxic effects; considered nontoxic by ingestion	151
CG 1.1% in medicated lotion	Rat	5	>10	No deaths, no toxic effects; considered nontoxic by ingestion	152
CG 1.0% in paste mask	Rat	5	>15	No deaths, no toxic effects; considered nontoxic by ingestion	153
CG 0.5% in liquid eye liner	Rat	10	>5	No deaths, no toxic effects	154
CG 0.3% in moisturizer	Rat	10	>7 ml/kg	No deaths, no toxic effects	155

Inhalation

An acute inhalation study was conducted on HEC using 2 rats, 2 mice, and 2 guinea pigs. The animals were exposed to 0.19 mg HEC/L air for 6 h in a 70-L chamber. All animals were necropsied after a 5-day observation period. No mortalities, unusual behavioral reactions, significant body weight, or gross pathological changes were noted.[161]

Dermal

HPC, 0.8% in an antiperspirant, was tested for dermal toxicity. A single occlusive patch containing 5.0 g/kg HPC was applied to each of 6 rabbits. No deaths occurred and no dermal irritation or gross effects were noted at the 14-day necropsy. The product was considered nontoxic by a single dermal exposure at a dose 500 times the expected human exposure.[162]

Irritation

Ocular

HEC was evaluated for ocular irritation in two Draize tests. Each test was conducted on 8 rabbits: 4 rabbits had their eyes rinsed for 2 min after a 1-min exposure period, and 4 had unrinsed eyes. In the first test, 100 mg of 100% HEC was instilled into each rabbit eye. A dose of 0.1 ml of a 2% wt/vol solution of HEC in water was administered in the second test. Eyes were scored according to Draize at 1, 24, and 72 h and 7 days. Mean scores at 1 h for the rinsed and unrinsed eyes of those rabbits receiving 100% HEC were 4.0 and 10.0 (max = 110), respectively; means at all subsequent readings were 0. Those rabbits receiving 2% (wt/vol) HEC had 1-h means of 2.5 and 2.0 for the rinsed and unrinsed eyes, respectively; means at all subsequent readings were 0. Thus, HEC was initially minimally irritating to rabbit eyes; however, all irritation had cleared by 24 h[163,164] (Table 4).

Laillier et al.[165] developed an objective method to measure corneal and conjunctival edema in the rabbit by determination of dry tissue weight and to measure vascular leakage in the conjunctiva and aqueous humor by dye diffusion. Aqueous solutions of HEC in concentrations of 0.5 and 1.0%, along with other organic solvents, were tested in single and repeated topical applications. Four albino rabbits were used for each solution. Applications of 0.1 ml were instilled into the conjunctival sac of both eyes of each rabbit 1, 3, 6, 7, and 13 times over the following periods: 2, 4, 7, 26, and 50 h. The rabbits were also given 50 mg/kg Evans blue dye solution by injection into the marginal ear vein 1 h after the last instillation of the test solution. The content of Evans blue in aqueous humor and conjunctiva was assayed 1 h after the dye injection. Assays were conducted to evaluate the corneal and conjunctival edema; tissues, corneas, and conjunctivae were dried by overnight immersion in acetone and subsequent storage over silica gel in a vacuum desiccator for 24 h.

After one instillation, 0.5% HEC had no significant effect on the eyes; 1% HEC was one of the lowest ranking compounds causing some irritation. Following repeated administration, both HEC solutions were given the lowest irritancy ranking. Statistically significant findings included: increase in μg Evans blue/g dry

weight of conjunctivae after 6 instillations of 0.5% HEC, increase in μg Evans blue/ml aqueous humor after 3, 7, and 13 instillations of 0.5% HEC, increase in μg Evans blue/ml aqueous humor after 1 instillation of 1.0% HEC, increase in μg Evans blue/g dry weight of conjunctivae after 3, 6, and 13 instillations of 1.0% HEC, and a decrease in percent dry weight of conjunctivae after 3 administrations of 1.0% HEC[165] (Table 4).

An ocular irritation test was conducted on HEC (2%; two samples), HPC (2%), MC (2%; three samples), and CG (1, 4, and 10%). Aqueous solutions of each cellulose derivative were prepared and preserved with sodium paraben (0.15%) and propylparaben (0.05%). Groups of 6 male albino rabbits were administered 0.1 ml of each solution in the conjunctival sac of the right eye, the other eye serving as a control. Readings were taken at 1 h, 1, 2, 3, 4, and 7 days after administration; observations were made with the unaided eye, ophthalmoscope, and/or slit lamp. Reactions were graded on a scale of 0 to 110 and the Acute Ocular Irritation Index (AOII) was calculated for each sample. The AOIIs ranged from 5.33 to 10.50 (max = 110). No lesions of the ocular mucous membrane were noted. The investigators concluded that HEC, HPC, MC, and CG, under these conditions, were slightly irritating[9] (Table 4).

HPC (50 mg) was instilled into both eyes of 2 rabbits to evaluate ocular irritancy. One eye of each animal was rinsed after a 1-min exposure. The eyes were scored according to Draize; all eyes had a score of 0 by 24 h. Slight irritation was noted in both unrinsed eyes at 1 h[166] (Table 4).

The Draize method was also used to evaluate the irritancy of 0.5 and 1.0% aqueous solutions of HPC in rabbits. A 0.1 ml sample of each solution was instilled into one eye of each of 3 rabbits; the other eye received a saline solution as a negative control. Isopropyl alcohol was administered to 3 rabbits as a positive control. The Draize score for each HPC solution was 0; the positive control had a score of 22.7. HPC was considered nonirritating[110] (Table 4).

A 5 mg HPC-soluble ocular insert was evaluated for irritation, ease of insertion, and retention time in both eyes of 12 beagles. Each dog received an insert at three different conjunctival sites for 5-day periods. Each test period was separated by 2 rest days. The inserts in the conjunctival cornices did not irritate the cornea and conjunctiva. Conjunctival hyperemia and chemosis were observed in 5 eyes with inserts beneath the nictitating membrane; however, this was attributed to the trauma caused by the difficult placement of these inserts[167] (Table 4).

MC, in a 1–2% solution, failed to produce irritation to the conjunctival membrane of a rabbit.[1]

HPMC was evaluated for ocular irritancy in 1 rabbit. A 0.1 mg sample of HPMC (solid) was instilled into one eye for a 30-sec exposure. The eye was then rinsed with water for 2 min. The other eye then received a similar sample but was not rinsed. Slight conjunctival irritation was noted after application. The eyes were completely healed within 48 h. It was concluded that the solid material may cause slight transient eye irritation[168] (Table 4).

CG was evaluated for ocular irritancy in 2 Draize tests. A 0.1 mg sample of CG (in water) was applied to the left eye of 6 rabbits in the first test, and a 0.01 g sample (solid) was similarly applied in the second test. None of the treated eyes was rinsed and the right eye of each animal served as the control. Eyes were scored at 1 min, 1, 24, and 72 h, and 4 and 7 days. All eyes had a score of 0 (max

TABLE 4. Ocular Irritation

Ingredient	*Animal*	*No. of animals*	*Method*	*Results*	*Reference*
HEC 100% (100 mg)	Rabbit	8—4 rinsed 4 unrinsed	Draize[a]	Scores of 4 and 10 for the rinsed and unrinsed eyes, respectively, at 1 h; all subsequent scores = 0; nonirritating	163
HEC 2% in aqueous solution	Rabbit	8—4 rinsed 4 unrinsed	Draize	Scores of 2.5 and 2.0 for the rinsed and unrinsed eyes, respectively, at 1 h; all subsequent scores = 0; nonirritating	164
HEC 0.5 and 1.0% in aqueous solution	Rabbit	8	Objective method using dry tissue weight and dye diffusion	Low irritancy after single and repeated administration	165
HEC 2% in aqueous solution (2 samples)	Rabbit	6 6	Official French method	AOIIs[b] of 6.17, slightly irritating 7.50, slightly irritating	9
HPC 100% (50 mg)	Rabbit	2—both eyes treated 1 rinsed 1 unrinsed	Draize	Slight irritation in unrinsed eyes at 1 h; all eyes with score of 0 at 24 h	166
HPC 2% in aqueous solution	Rabbit	6	Official French method	AOII of 7.33, slightly irritating	9
HPC 0.5 and 1.0% in aqueous solution	Rabbit	6	Draize	Total score of 0 for each solution; nonirritating	110
HPC 5 mg	Beagle	12	Soluble ocular inserts	Nonirritating	167
MC 2% in aqueous solution (3 samples)	Rabbit	6 6 6	Official French method	AOIIs of 6.83, slightly irritating 8.17, slightly irritating 10.50, slightly irritating	9
MC 1–2% solution	Rabbit	1	–	No irritation	1

HPMC 100% (0.1 mg)	Rabbit	1—both eyes treated 1 rinsed 1 unrinsed	Single instillation	Slight conjunctival irritation noted after application; eyes healed in 48 h; concluded that solid material may cause slight transient eye irritation	168
CG 1, 4, and 10% in aqueous solution	Rabbit	6 6 6	Official French method	AOIIs of (1%) 5.33, slightly irritating (4%) 7.83, slightly irritating (10%) 6.17, slightly irritating	9
CG 0.1 mg in aqueous solution	Rabbit	6	Draize	All eyes had score of 0 by day 3	169
CG 100% (0.01 g)	Rabbit	6	Draize	All eyes had score of 0 by day 4	170
CG 3.0% in wrinkle-smoothing preparation	Rabbit	6	Modified Draize	Average irritation score at day 1 = 0; nonirritating	171
CG 1.1% in a medicated lotion	Rabbit	6	Modified Draize	Average irritation score at day 1 = 1; day 2 = 0; minimally irritating	172
CG 1.0% in paste mask	Rabbit	6	Modified Draize	Average irritation score at day 1 = 0; nonirritating	173
CG 0.5% in liquid eyeliner	Rabbit	9—3 rinsed 6 unrinsed	Draize	No ocular reactions; nonirritating with or without rinse	174
CG 0.3% in moisturizer	Rabbit	6	Single instillation	Slight conjunctival redness noted after 1 h, but clear by 24 h; no effect on corneal and iridial membranes	155
CMC 0.605% in eye makeup product	Rabbit	6	Single instillation	2/6 had score of 1 (max = 4) at 24 and 48 h; all 0 at 72 h; nonirritating	175

[a]Maximum score = 110
[b]AOII, acute ocular irritation index; max = 110.

= 110) by 3 and 4 days in the first and second tests, respectively[169,170] (Table 4).

Various cosmetic products containing CG or CMC ranging in concentrations of 0.3 to 3.0% were nonirritating to minimally irritating in rabbit eyes. Specific results are given in Table 4.

Dermal

A primary skin irritation test was conducted on HEC (2%; two samples), HPC (2%), MC (2%; three samples), and CG (1, 4, and 10%). Aqueous solutions of each cellulose derivative were prepared and preserved with sodium paraben (0.15%) and propylparaben (0.05%). Each solution (0.5 ml) was applied on two patch areas, the right (scarified) and left (intact) flanks of male albino rabbits (6/group). Patches were occluded for 23 h, removed, and readings (scale of 0 to 8) taken 1 and 48 h later. The Primary Irritation Indices (PII) ranged from 0.04 to 0.21 (max = 8). HEC, HPC, MC, and CG, under these conditions, were nonirritating[9] (Table 5).

A cutaneous tolerance test was also conducted on this same group of cellulose solutions. Aqueous solutions of 2% HEC (two samples), 2% HPC, 2% MC (three samples), and 1, 4, and 10% CG were prepared and preserved with sodium paraben (0.15%) and propylparaben (0.05%). Male albino rabbits (3/group) had 2 ml of each solution applied on the clipped right and left flanks. Each sample was spread uniformly by hand and given a light 30-sec massage. Applications were made five times per week for 6 weeks. Clipping was repeated as needed each Monday, 6 h prior to application. Daily scorings were taken prior to each application. Recovery was studied for 7 days after the last administration. Two biopsies taken from each rabbit at 6 weeks were examined microscopically. The Mean Maximum Cutaneous Irritation Indices (MMII) ranged from 0 to 1.00 (max = 8). The investigators classified these samples as well tolerated and nonirritating to relatively well tolerated and slightly irritating[9] (Table 5).

HEC is used in a thixotropic composition for prophylactic treatment of bovine mastitis. It forms a film on the teat and provides a physical barrier to bacteria. When tested on milking cows, no signs of irritation were observed.[176] Teats of cows protected by a similar composition containing HEC after twice-daily milking for 8 months also had no signs of irritation[76] (Table 5).

An antiperspirant containing 0.8% of HPC was tested for primary skin irritation. A 0.5 ml sample of the product was applied with an occlusive 24-h patch to the clipped intact and abraded skin of each of 6 rabbits. Sites were scored 24 and 72 h after application. A marketed antiperspirant was evaluated as a control. PIIs of 0.0 and 0.2 (max = 8) were obtained on the intact and abraded skin, respectively. The product was considered mildly irritating[177] (Table 5).

HPMC (full strength) was evaluated for skin irritation in 2 rabbits. Ten applications were made over 14 days to the shaved abdomen of each rabbit. The treated sites were covered with gauze pads so that contact with the skin was continuous for 2 weeks. One rabbit received applications with dry solid HPMC, and the other received HPMC moistened with water. Each rabbit additionally received HPMC applications daily for 3 days on an abraded skin site. No skin irritation was observed from contact with the dry material. The moistened HPMC produced a slight redness believed to be due to the material sticking to the skin. There was no evidence of systemic injury. Solid HPMC was essentially nonirritating and not absorbed through the skin in harmful amounts[178] (Table 5).

A facial cleanser containing 1.1% HPMC was evaluated for skin irritation in 4 rabbits. A 0.5 ml sample of the cleanser (10% in an aqueous solution) was applied with a 24-h occlusive patch to the shaved skin of each rabbit on both intact and abraded sites. Sites were scored according to Draize at 24 and 72 h. The cleanser gave a PII of 0.6 (max = 8)[179] (Table 5).

Application of CG or CMC to the shaved abdominal area of rabbits five times per week for 4 weeks produced no signs of skin irritation[1] (Table 5).

Cosmetic products containing from 0.3 to 3.0% CG or CMC were found nonirritating to slightly irritating when applied topically to the skin of rabbits (see Table 5 for specific results).

Mucous Membrane

A moisturizing cream containing 0.3% CG was tested for mucosal irritation in 6 rabbits. Each rabbit (3 males and 3 females) received a 0.1 ml topical application to the genital mucosa. No signs of irritation were noted during the 7-day study.[155]

Subchronic Toxicity

Oral

Diets containing 0.2, 1.0, and 5.0% HEC were fed to three groups of 20 rats for 90 days. Two groups/sex were kept as controls. Feed consumption and weight gain were monitored weekly; behavior was checked daily. Blood and urine samples were collected from 5 males and 5 females in each group on days 0, 21, 45, and 90. Necropsy was performed on all animals, and tissues were examined microscopically from 5 males and 5 females from both control groups and the 1.0 and 5.0% groups. No significant findings attributable to ingestion of HEC were noted.[184]

HPC (of low substitution) was administered by stomach tube to groups of 5 male and 5 female rats for 30 days. HPC was suspended in 1% gum arabic solution and administered at doses of 1.5, 3.0, and 6.0 g/kg per day. No remarkable changes were noted in growth, organ weights, hematological and urinary analyses, or tissue alterations.[143]

The oral toxicity of HPC was evaluated in rats fed a diet containing the cellulose derivative at a concentration of 0.2, 1.0, or 5.0% for 90 days. Each test group consisted of 5 male and 5 female rats. Control groups received 0.2, 1.0, or 5.0% cellulose diets. No differences between the control and treated groups were noted in survival, growth, behavior, food consumption and utilization, hematopoietic and urinary function analyses, organ weights and organ weight ratios, or in the gross and microscopic examination of tissues.[185]

No adverse effects were noted in chicks fed a diet containing 2% MC for 20–21 days.[1]

No toxic effects were observed in rats given 0.5 g/kg MC (method unspecified) for 4 weeks. Rats ingesting MC at a dose of 11.4 g/kg per day for 95 days had no significant pathological changes; however, growth of females was decreased about 14%, apparently due to a decrease in food intake. Growth of males was normal. Similarly, rats fed a 50% MC diet for 90 days had significant

TABLE 5. Skin Irritation

Ingredient	*No. and type of animal*	*Method*	*Results*	*Reference*
HEC 2% in aqueous solution (2 samples)	6 rabbits 6 rabbits	23-h occlusive patch on intact and abraded skin	PIIs[a] of 0.08, nonirritating 0.13, nonirritating	9
HEC 2% in aqueous solution (2 samples)	3 rabbits 3 rabbits	Repeated applications 5 times per week for 6 weeks	MMIIs[b] of 0.34, nonirritating and well tolerated 1.00, slightly irritating and relatively well tolerated	9
HEC in thixotropic composition	Cow	Repeated application to the teat up to 2 times daily for 8 months	No irritation	76,176
HPC 2% in aqueous solution	6 rabbits	23-h occlusive patch on intact and abraded skin	PII of 0.13, nonirritating	9
HPC 2% in aqueous solution	3 rabbits	Repeated applications 5 times per week for 6 weeks	MMII of 0.67, slightly irritating and relatively well tolerated	9
HPC 0.8% in an antiperspirant	6 rabbits	24-h occlusive patch on intact and abraded skin	PIIs of 0.0 (intact) 0.2 (abraded), considered mildly irritating	177
MC 2% in aqueous solution (3 samples)	6 rabbits 6 rabbits 6 rabbits	23-h occlusive patch on intact and abraded skin	PIIs of 0.04, nonirritating 0.08, nonirritating 0.21, nonirritating	9
MC 2% in aqueous solution (3 samples)	3 rabbits 3 rabbits 3 rabbits	Repeated applications 5 times per week for 6 weeks	MMIIs of 0, nonirritating and very well tolerated 0.34, nonirritating and well tolerrated 0.67, slightly irritating and relatively well tolerated	9
HPMC 100%	2 rabbits	10 applications over 14 days for continuous 2 week contact on intact skin; 3 daily applications on abraded skin	No irritation noted with dry solid; moistened application caused slight redness; no systemic injury; considered essentially nonirritating	178

HPMC 1.1% in facial cleanser (tested 10% in aqueous solution)	4 rabbits	24-h occlusive patch on intact and abraded skin	PII of 0.6; essentially nonirritating	179
CG 1, 4, and 10% in aqueous solution	6 rabbits 6 rabbits 6 rabbits	23-h occlusive patch on intact and abraded skin	PIIs of 0 (1%), nonirritating 0.08 (4%), nonirritating 0 (10%), nonirritating	9
CG 1, 4, and 10% in aqueous solution	3 rabbits 3 rabbits 3 rabbits	Repeated applications 5 times per week for 6 weeks	MMIIs of 1.00 (1%), slightly irritating and relatively well tolerated 0.67 (4%), slightly irritating and relatively well tolerated 0.34 (10%), nonirritating and well tolerated	9
CG unspecified concentration	Rabbit	Repeated applications 5 times per week for 4 weeks	No irritation	1
CG 3.0% in wrinkle-smoothing preparation	9 rabbits	24-h occlusive patch to intact skin	AIS[c] = 0, nonirritating	180
CG 1.1% in medicated lotion	9 rabbits	24-h occlusive patch to intact skin	AIS = 0.67, slightly irritating	181
CG 1.0% in paste mask	9 rabbits	24-h occlusive patch to intact skin	AIS = 0.17, minimally irritating	182
CG 0.3% in moisturizing cream	3 rabbits	Daily application for 4 days	PII of 1.6, slight erythema developed and persisted for 7-day period; 1 rabbit with slight edema	155
CMC 0.605% in eye makeup	6 rabbits	24-h open patch for 3 consecutive days to abraded skin	No reactions; nonirritating	183

[a]PII, Primary Irritation Index (max = 8)
[b]MMII, Mean Maximum Cutaneous Irritation Index (max = 8)
[c]AIS, Average Irritation Score (max = 4)

growth depression. This was attributed to the lack of nutrition in a "bulk"-producing diet and not to any toxic effect.[1]

Dogs fed up to 100 g MC daily for 1 month had no toxic effects.[1]

HPMC and MC were evaluated in a 90-day feeding study in rats and beagle dogs. Groups of 10 male and 10 female rats received diets containing 0, 1, 3, and 10% MC or HPMC with a nominal viscosity of 10 cp as well as 0, 3, and 10% MC or HPMC with a nominal viscosity of 4000 cp. Groups of 2 male and 2 female beagle dogs received diets containing 0, 2, and 6% HPMC with a nominal viscosity of 10 cp. No evidence of toxicity was observed in rats or dogs as judged by mortality, body weights, feed consumption, urine analyses, hematological evaluations, serum components values, organ weights, or gross or microscopic alterations.[186]

HPMC, in two studies, was fed to rats for 90 days at doses ranging from 0.3 to 20% in the diet. Moderate growth retardation was noted in the males fed the 10 and 20% diets in both studies; the females (one study only) fed the 20% diet also showed this growth retardation. A decrease in feed efficiency was noted with the 20% diet in both sexes. In one study, 6 of the 20 rats fed the 20% HPMC diet died of undetermined causes. No lesions were seen in any tissue from these rats.[1]

Groups of 20 rats were fed HPMC at concentrations of 0, 2, 10, and 25% for 30 days. The highest dose produced weight loss, early deaths, and severe diarrhea. Urinary and hematological values were normal except for a decreased red blood cell count in the high-dose group. Organ weights were normal, and no lesions were found.[1]

Rabbits (6 per group) fed HPMC for 30 days at concentrations of 0, 2, 10, and 25% had no toxic effects. Urinalyses and organ weights were normal, and no lesions were observed.[1]

Two dogs were fed 25 or 50 g HPMC daily for 30 days. The dog fed 50 g HPMC had weight loss, diarrhea, and anemia. Urinalyses, organ weights, and organs were normal in both dogs.[1]

HPMC of low viscosity was evaluated for toxicity in rats and dogs. Groups of 15 male and 15 female rats and groups of 4 male and 4 female beagle dogs were fed diets containing 0, 1, or 5% HPMC for 90 days. No significant toxic effects were noted with respect to mortality, body weights, feed consumption, urinalyses, hematological and clinical chemistry values, and necropsy and histopathological examinations.[187]

No adverse effects were noted in chicks fed a diet containing 2% CG for 20 days.[1]

No toxic effects were noted in rats fed 0.3 or 0.5 g CG daily for 2 months or in rats fed a diet containing 14% CG for 5 weeks. Rats fed a diet containing either 20% CG or CMC for 63 days also had essentially no toxic effects. A slight decrease in growth was observed in the rats receiving 20% CG, although this was attributed to a decrease in nutrient food intake resulting from the bulkiness of the diet.[1]

Five dogs were given doses of CG increasing from 12.5 to 31 to 47 mg/kg daily over a period of 3–4 months. No gross pathological changes were observed. Uptake of CG into the reticuloendothelial cells of the aorta was observed at microscopic examination.[1]

Rats were fed a hypercholesterolemic diet both with and without 5% CMC for 8 or 14 days in order to evaluate the hypocholesterolemic effect of CMC. CMC depressed plasma and liver cholesterol concentrations compared to controls; however, it did not alter cholesterol absorption from the gut.[1]

Intravenous

HEC (three viscosity grades) was injected iv into groups of 2 dogs without producing any acute or serious reactions. All dogs received five injections per week of an isotonic HEC solution for 6–12 weeks. Concentrations of HEC administered ranged from 2.3 (high-viscosity solution) to 10.0% (low-viscosity solution). The high-viscosity solution produced marked anemia, leukopenia, and increased sedimentation rate and plasma viscosity. The medium-viscosity solution produced the most pronounced hemodiluting effect and an increased sedimentation rate. No treatment-related lesions were observed in the high- and medium-viscosity groups. HEC storage in the hepatocytes and the glomerular endothelial cells, as well as atheromatous and fibrous intimal lesions and medial degenerations and calcifications, were most extensive in dogs of the low-viscosity group. These reactions were entirely absent in the high-viscosity group.[188]

Hueper[160] found that repeated iv doses of CMC to dogs resulted in a decrease in blood hemoglobin and an increase in sedimentation rate. CMC was stored in the Kupffer cells, the reticular cells of the spleen, the endothelial cells of the glomeruli, and on the walls of the aorta and its branches.

Dermal

A wrinkle smoother product containing 3.0% CG was evaluated for dermal toxicity in rats. Fifteen rats (males and females) received a daily dose of 886 mg/kg (0.9 ml/kg) of the product 5 days per week for 13 weeks. This was a dose set at 100 times the average daily human use level. Control groups consisted of untreated rats and rats treated with ethanol. Each dose was applied by inunction to an anterior dorsal shaved site on each rat. The product was wiped off 1 h after application because the active agent, sodium silicate, was a known irritant. No significant adverse effects were noted in mortality, body weights, hematological values and urinalyses, organ weights, and gross and microscopic examination. Scattered transient minimal skin irritation was noted in most test animals during weeks 2 through 6. The investigators concluded that the product was safe for marketing.[189]

A lotion containing 1.1% CG was similarly evaluated for dermal toxicity in rats. Ten male and ten female rats received a daily dose of 2900 mg/kg (2.9 ml/kg) of the lotion 5 days per week for 13 weeks. This was a dose set at 100 times the average daily human use level. Control rats were treated with distilled water. Each dose was applied by inunction to an anterior dorsal shaved site on each rat. No significant adverse effects were noted in mortality, body weights, appearance and behavior, hematological values and urinalyses, or gross and microscopic examinations. The lotion was not systemically toxic and did not produce any abnormal cumulative dermal effects.[190]

Chronic Toxicity

Oral

A 2-year chronic oral toxicity test was conducted by Smyth et al.,[141] in which groups of 32 Wistar strain rats, 16 males and 16 females, each received diets containing 0.2, 1, and 5% HEC. The resulting mean dosages were, respectively, 0.09, 0.41, and 2.31 g/kg per day. Offspring were kept until at least 10 of each sex representing 10 litters from each dosage group had attained a weight of 40 g. These rats were maintained on the test diet until the end of the study, bringing the total number of rats for each dosage group to 52. A control group was maintained on the basic diet, free of HEC. Criteria evaluated included growth, food intake, life span, frequency of infections, body weights, kidney and liver weights, number of litters, hematological values, incidence of neoplasms, and microscopic alterations of numerous organs.

Forty-eight percent of the rats died during the 2-year period; however, the investigators found "every death was caused by a recognizable factor distinct from the doses" and that fatalities were evenly distributed over the test and control groups. The food intake of the rats fed the 5% HEC diet was one-tenth greater than that of the other groups. Their feces were noted to be almost white and bulkier than normal due to the large content of undigested cellulose ether. None of the other criteria evaluated revealed any relationship between dose and response[141] (Table 6).

HPC of low substitution was administered to groups of 5 male and 5 female rats by stomach tube at a daily dose of 1.5, 3.0, or 6.0 g/kg for 6 months. HPC was suspended in a 1% gum arabic solution, and control groups received a similar dose of the vehicle. A slight decrease in body weight was observed in the males and females at 7–8 weeks. Some variations were noted in organ weights and organ weight ratios; however, these were distributed randomly and did not have a dose-response relationship. No other significant effects were observed in behavior, feed consumption, hematological values and urinalyses, or in histopathological examinations[143] (Table 6).

In studies conducted prior to 1973, no toxic effects were noted in rats fed up to 5.0% MC for 184 days or in rats fed 1.8% MC for 8 months[1] (Table 6).

MC was also evaluated for toxicity in a 2-year feeding study. Groups of 50 male and 50 female rats were fed diets containing 1 or 5% MC with nominal viscosity of 15, 400, or 4000 cp. Control groups of 40 male and 40 female rats were fed the basal diet. No evidence of treatment-related effects was observed in mortality, body weights, feed consumption, hematological values, serum components values, organ weights, gross and microscopic examinations, or in tumor incidence[186] (Table 6).

In studies conducted prior to 1973, rats were fed diets containing up to 30% HPMC for periods up to 2 years. No significant toxic effects were noted other than growth retardation at concentrations of HPMC ranging from 20 to 30%. This has been attributed to malnutrition due to the nonnutritive bulk content of this diet. No toxic effects were noted in gross and microscopic pathology. Dogs fed up to 3 g/kg per day of HPMC also showed no toxic effects[1] (Table 6).

In studies conducted prior to 1973, rats and mice were fed diets containing 0 and 5% CMC for periods of 8 months–1 year (rats) and from weaning to death (mice). No toxic effects were noted[1] (Table 6).

CG has been evaluated for oral toxicity in rats, mice, guinea pigs, and dogs in numerous studies prior to 1973. Both rats and dogs were fed diets containing 0.5 and 1.0 g/kg CG for 6 months, whereas guinea pigs were administered this same dosage for 6 months and 1 year. No toxic effects were observed. Other rats received a diet containing 5% CG for 8 months; no toxic effects were noted. In another study, rats and mice were fed diets containing 0, 1, and 10% CG for 104 and 100 weeks, respectively. Deaths in the first 1½ years were due to pulmonary infection; later deaths were attributed to neoplasms common to aging rats and mice. There was no indication of CMC absorption or storage. Tumor frequencies were normal. A retardation in growth was observed in the rats receiving 10% CG, although it was noted that these rats also had a higher feed intake[1] (Table 6).

In unpublished studies, CG was evaluated for oral toxicity in dogs, guinea pigs, and rats. Diets containing 2, 5, 10, and 20% CG were fed to groups of 3 mongrel dogs for 6 months. Mortality, body weight, hematological and urinary parameters were monitored. Those dogs on the 20% diet "starved due to interference with food intake." No evidence of other toxic or metabolic effects was noted[191] (Table 6).

Groups of 20 guinea pigs were fed diets containing 0 (15 guinea pigs only), 0.5, and 1.0 g/kg CG for 1 year. No effects were noted in growth or at necropsy[192] (Table 6).

Groups of 25 rats (males and females) were fed diets containing 0, 0.1, 0.5, and 1.0 g/kg CG for 25 months. No significant differences were noted between the controls and test animals in urinalyses, hematological values, fertility (through three generations), or findings at necropsy. No neoplasms were found in the test rats[193] (Table 6).

Sensitization

HPMC was evaluated for sensitization using the Magnusson-Kligman guinea pig maximization test. Thirty guinea pigs were used: 10 experimental, 10 untreated, and 10 positive controls treated with mercaptobenzothiazole. Each animal received three intradermal injections into the shaven shoulder consisting of 0.1 ml of 50% complete Freund's adjuvant in saline, 0.1 ml of 1% HPMC in saline, and 0.1 ml of 1% HPMC in 50% complete Freund's adjuvant in saline. One week later, the same area was pretreated with 10% sodium lauryl sulfate (SLS) in petrolatum and occlusively patched for 48 h with 25% HPMC in petrolatum. Following a 2-week rest, a 24-h occlusive challenge patch containing 25% HPMC in petrolatum was applied to the shaven flank of each animal. The control guinea pigs also received the challenge aplication. Reactions were scored 24 and 48 h after patch removal. HPCM did not produce any responses indicative of sensitization and was considered a nonsensitizer.[194]

HPMC was further evaluated for sensitization in Hartley albino guinea pigs by use of a modified Maguire method. Ten male guinea pigs each received a 0.1 ml application to the clipped back of 2% HPMC in aqueous solution. This was repeated for a total of four applications in 10 days. At the time of the third application, a 0.2 ml sample of Freund's adjuvant was injected intradermally at several points adjacent to the insult site. After a 2-week nontreatment period, challenge applications were made to previously untested sites. Ten guinea pigs were

TABLE 6. Chronic Oral Toxicity

Ingredient	*Concentration/dose (in diet)*	*Animal, No.*	*Length of administration*	*Results*	*Reference*
HEC	0.2, 1, and 5% equivalent to 0.09, 0.41, and 2.31 g/kg per day	Rats, 32 per group (16 male/16 female); offspring were maintained on test diet for a total of 52 rats per dose	2 years	Mortalities unrelated to HEC administration; food intake on 5% diet slighly increased; feces white and bulky	141
HPC in 1% gum arabic solution	0, 1.5, 3.0, and 6.0 g/kg per day (by stomach tube)	Rats, 10 per group (5 male/5 female)	6 months	Slight decrease in body weight at 7–8 weeks; no other significant toxic effects	143
MC	0, 1.66, 1.66 and 5.0%	Rats, 5 per group (3 groups female/one group male)	184 days	Slight increase in feed intake and weight gain; no gross or pathological effects	1
MC	1.8% (in diet and drinking water) equivalent to 436 mg/per rat	Rats, 80	8 months	No toxic effects	1
MC of nominal viscosity 15, 400, and 4000 cp	0, 1, and 5% of each viscosity	Rats, 100/per group (50 male/50 female)	2 years	No toxic effects	186
HPMC	0, 1, 3, 10, and 30%	Rats, 20 per group (10 male/10 female)	121 days	Marked decrease in growth at 30% level; 50% mortality at 30% level; slight growth decrease in 10% males; no pathological effects; malnutrition due to nonnutritive bulk in diet	1
HPMC	0, 20, and 25%	Rats, 20 per group	1 year	Growth retardation at both levels; no other toxic effects	1
HPMC	0, 1, 5, and 20%	Rats, 100 per group (50 male/50 female)	2 years	High-dose group showed growth reduction in first year; all others normal; trend continued in second year; no significant microscopic effects or tumors	1

HPMC	0, 0.1, 0.3, 1, and 3 g/kg per day	Dogs, 2 per group	1 year	No toxic effecs	1
CMC	0 and 5%	Rats, 25 per group (10 male/15 female)	8 months	No toxic effects	1
CMC	0 and 5%	Rats, 10 per group (male and female)	1 year	No toxic effects	1
CMC	0 and 5%	Mice, 5 at 0% 10 at 5%	From weaning to death	No toxic effects	1
CG	0, 0.5, and 1.0 g/kg per day	Rats, 100 per group	6 months	No toxic effects	1
CG	0, 0.5, and 1.0 g/kg per day	Guinea pigs, 100 per group	6 months	No toxic effects	1
CG	0, 0.5, and 1.0 g/kg per day	Dogs, 10 per group	6 months	No toxic effects	1
CG	0.5 and 1.0 g/kg per day	Guinea pigs, 20 per group	1 year	No toxic effects	1
CG	0 and 5%	Rats, 25 per group (10 male/15 female)	8 months	No toxic effects	1
CG	0, 1, and 10%	Rats, 100 per group (50 male/50 female)	2 years	Slight growth retardation at 10% level, although they had a higher feed intake; mortalities in first 1½ years due to pulmonary infection; later deaths due to neoplasia common to aging animals; no indication of CMC absorption or storage; tumor frequency normal	1
CG	0, 1, and 10%	Mice, 100 per group (50 male/50 female)	100 weeks	Mortalities in first 1½ years due to pulmonary infection; later deaths due to neoplasia common to aging animals; no indication of CMC absorption or storage; tumor frequency normal	1
CG	2, 5, 10, and 20%	Dogs, 3 per group	6 months	Dogs on 20% diet "starved due to interference with food intake"; no evidence of other toxic or metabolic effects	191
CG	0, 0.5, and 1.0 g/kg per day	Guinea pigs, 20 per group	1 year	No toxic effects	192
CG	0, 0.1, 0.5, and 1.0 g/kg per day	Rats, 25 per group (male and female)	25 months	No toxic effects	193

similarly tested with a positive control. No responses were noted on challenge with HPMC, whereas the positive controls responded with moderate to severe redness. The negative response by guinea pigs would indicate that humans would not be sensitized by HPMC.[195]

Phototoxicity

A phototoxicity test was conducted on a mascara containing 0.4% HEC. A 0.25 ml dose of the mascara was applied to the shaved skin of each of 6 albino rabbits. A positive control group received applications of 8-methoxypsoralen. The rabbits were then exposed to UV light at a distance of 8 inches from the skin (some of the sites were covered). No irritation was produced by the mascara at either the irradiated or nonirradiated sites. The product was nonphototoxic when compared to the positive control.[196]

A liquid eyeliner containing 0.5% CG was evaluated for phototoxicity in albino rabbits. Two occlusive patches containing samples of the eyeliner were applied to the shaved back of each of 6 rabbits. One rabbit received two patches of 8-methoxypsoralen as the positive control. After 2 h, one patch on each animal was removed and the site was irradiated with a Sylvania No. F40-BLB lamp. The other sites were protected by aluminum foil. The irradiated sites were then repatched and covered with an occlusive binder. All patches were removed at 48 h and scored at 49, 72, and 96 h. Nonirradiated sites produced a mean irritation score of 0.22 (max = 8); irradiated sites had a mean phototoxic irritation score of 0.39 (max = 8); both were considered minimally irritating. The product was concluded to be minimally irritating but not phototoxic to the skin of rabbits.[197]

Teratogenicity/Reproduction Studies

Groups of 11–13 mice were injected ip on days 3–7 or 8–12 of pregnancy with 10 ml/kg physiological saline, sesame oil, 1 or 4% HEC. Teratological effects were determined on day 19. Fetal resorption was significantly increased by HEC at both concentrations when administered on days 3–7; there were 18.7 and 43.8% resorptions for 1 and 4% HEC, respectively, compared to 8.3% for the saline control and 5.1% for the sesame oil. Weights of the surviving fetuses in the 4% HEC group administered on days 3–7 were significantly increased. This same group had 10.20 and 10.53% gross visceral and skeletal deformities, respectively, compared to 1.98 and 1.96% for the saline control, 4.65 and 9.76% for the 1% HEC solution, and 1.39 and 8.57% for the sesame oil. All groups receiving the HEC solutions had a lower percentage of fetuses with additional ribs than the saline control.[198]

Kitagawa et al.[199,200] studied the teratological effects of HPC in both rabbits and rats. Doses of 0, 200, 1000, and 5000 mg HPC/kg per day were administered by stomach tube to groups of 12, 11, 11, and 12 Himalayan rabbits, respectively, on days 6–18 of gestation. HPC was suspended in 1% gum arabic solution; controls received 10 mg/kg of the vehicle. The low dose represented 10 times the human use level, and the high dose was the largest amount of substance technically possible to administer by stomach tube. Cesarean sections were performed

on the 29th day of gestation. All of the fetuses were examined for skeletal and organ malformations. No embryotoxic or teratogenic effects were noted, and no adverse influence on behavior, appearance, and growth of the maternal rabbits was observed.

Wistar rats received similar doses of HPC, 0, 200, 1000, and 5000 mg/kg per day by stomach tube on days 7–17 of gestation. HPC was suspended in 1% gum arabic solution; the controls received 62.5 ml/kg of the vehicle. The low and high doses represented 10 and 250 times the human use level, respectively. On day 21 of gestation, cesarean sections were performed on 21–24 rats in each dose group; the remaining 12–15 rats in each dose group were allowed to deliver spontaneously. Those pups delivered spontaneously were weaned at 28 days, and 2 males and 2 females from each litter were randomly selected for F_1 generation reproduction studies. No significant embryotoxic or teratogenic effects nor abnormalities in fetal skeletal development and F_1 generation reproductive abilities were noted.[200]

In two separate studies, three generations of rats were fed basal diets containing up to 5% MC. These rats consumed more feed than the controls and had increased body weights. No significant adverse effects were noted on reproductive function. At gross and microscopic examination of the first generation animals (in one study), no tissue damage was observed.[1]

Pregnant rabbits were fed diets containing 0.25–0.5% MC on days 9–16 of gestation. No teratological effects were noted; however, some fetal toxicity was observed.[2]

MC, in corn oil, was administered by intubation to pregnant mice, rats, and hamsters. Doses of 345 mg/kg MC given to mice on days 6–15 of gestation produced no effects on nidation or maternal or fetal survival. Doses of MC (1600 mg/kg per day) similarly administered to mice produced no clear evidence of teratological effects; however, this dose did produce an increase in maternal mortality and number of resorptions and a decrease in pregnancy rate and fetal growth. These latter effects were attributed to the administration of a dose essentially equal to an LD_{50}, even though administered over a period of 10 days. Similar studies in rats and hamsters, administered doses up to 1320 and 1000 mg/kg per day for 10 and 5 days of gestation, respectively, produced no significant effects on nidation or maternal or fetal survival. Abnormalities in the soft or skeletal tissues of test and sham-treated controls were comparable.[2]

The teratogenicity and toxicity of MC were studied in CD/1 mice. Groups of 20 pregnant mice were administered MC doses of 0, 70, 153, 330, and 700 mg/kg by gavage on days 6–15 of gestation. The high dose was equal to 10% of the LD_{50}. MC was administered as a 1.2% suspension in corn oil; the negative control group received an equal volume dose of corn oil, and the positive controls received 150 mg/kg acetylsalicylic acid. The mice were killed on day 17 of gestation, and the urogenital tracks were examined at necropsy. Fetal abnormalities were determined by external, visceral, and skeletal examinations. No significant teratogenic or toxic effects were noted.[201]

The teratogenicity and toxicity of MC were similarly studied in Sprague-Dawley rats. Groups of 20 pregnant rats received MC doses of 0, 120, 260, 556, and 1200 mg/kg by gavage on days 6–15 of gestation. The high dose was equal to 10% of the LD_{50}. MC was administered as a 10% suspension in corn oil; the

negative control group received an equal volume dose of corn oil, and the positive controls received 250 mg/kg acetylsalicylic acid. The rats were killed on day 20 of gestation, and the urogenital tracks were examined. Fetal abnormalities were determined by external, visceral, and skeletal examinations. No significant teratogenic or toxic effects were noted.[202]

Three generations of rats were fed diets containing 0, 0.1, 0.5, and 1.0 g/kg CG. A slight increase in weight was observed in the treated animals. No significant adverse effects were noted in fertility, gross or microscopic lesions, urinalyses, and hematological values.[1]

Rats fed 5 ml of a 0.2% solution of CMC on the eleventh day of gestation showed an increase in resorption rate and in the number of malformed fetuses.[2]

MC, CG, and CMC have been used as vehicles and negative controls in various teratological studies. Concentrations ranged from 0.5 to 1.25% for MC,[203,204] 0.5 to 2% for CG,[205,206] and 1% for CMC.[207]

MUTAGENICITY AND CARCINOGENICITY

MC (50 μg) was nonmutagenic in the Ames test with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, both with and without metabolic activation.[208]

MC was evaluated for mutagenicity in three different test systems: a host-mediated assay (in vitro and in vivo), cytogenetic studies (in vitro and in vivo), and a dominant lethal assay (in vivo). In the host-mediated assay, no significant increase in mutant or recombinant frequencies was observed when MC was tested in vitro at a concentration of 10% or in vivo at doses up to 5000 mg/kg (in mice) using *S. typhimurium* strains TA1530 and G-46 and *Saccharomyces* D3, respectively. In the cytogenetic studies, rats administered orally up to 5000 mg/kg MC had no significant aberrations of the bone marrow metaphase chromosomes. No significant aberrations were noted in the anaphase chromosomes of human tissue culture cells exposed up to 800 mcg/ml MC. MC was nonmutagenic in the dominant lethal assay in rats dosed with up to 5000 mg/kg.[209]

CG was evaluated for mutagenicity in a series of short-term assays using *S. typhimurium* strains TA100 and TA98 and silkworms for mutations, *Bacillus subtilis* for rec assay (without metabolic activation), and hamster lung fibroblast cells for chromosomal aberrations (without metabolic activation). Results were negative for all tests; investigators concluded that CG was nonmutagenic.[210]

CMC was nonmutagenic in *S. typhimurium* strains TA100 and TA98 both with and without metabolic activation and in *Escherichia coli* strain WP-2 without metabolic activation.[211]

Twenty-five Bethesda black rats were injected subcutaneously with 500 mg of powdered MC and tissues were examined 2 years later. The tumor incidence was similar in treated rats and controls.[1]

Several studies have been conducted to evaluate the effects of MC on rats transplanted subcutaneously with Murphy-Sturm lymphosarcoma. Intraperitoneal injections of MC (2 ml of a 2.5% aqueous solution) produced a significant increase in the percentage of complete tumor regressions. A similar study in rats

transplanted with Walker tumor 256 gave no indication of beneficial effects due to MC.[1]

Weekly subcutaneous injections of 1 ml of a 2% CMC solution administered to 30 rats for 73 weeks produced tumors at the injection site in 43% of the animals. Deposits of CMC were also found at injection sites. The tumors were fibrosarcomas.[1]

CMC has been used as the vehicle and negative control in a bioassay of selenium sulfide. A 0.5% aqueous solution of CMC was administered by gavage to groups of 50 rats and 50 mice of each sex 7 days per week for 103 weeks. Dose volumes were 1 ml/kg body weight in rats and 10 ml/kg body weight in mice.[212]

CLINICAL ASSESSMENT OF SAFETY

Oral Toxicity

The World Health Organization[213] has established an acceptable daily intake for man of up to 25 mg/kg body weight for HPC, HPMC, MC, and CG; this intake level represents the sum total of modified celluloses.

Single oral doses of MC ranging from 0.6 to 8.9 g have produced only mild laxative or constipating effects in man. Daily doses of 1–6 g MC (max = 6 g for up to 240 days) were effective in the alleviation of chronic or acute constipation and produced no evidence of systemic changes or toxicity. Daily doses of 10 g MC were effective as a laxative.[1]

Similarly, CG has been administered orally as a laxative in large doses with no adverse effects other than mild abdominal discomfort or diarrhea. Twice daily oral doses of 2–12 g CG produced no serious side effects in 128 subjects. Daily doses of approximately 10 g CG for 6 months produced no hematological or toxic effects or mucosal irritation in 22 adults. CG administered as a laxative to 250 adults over a period of 3 years in twice daily doses of 2–18 g produced no toxic effects.[1,2]

Ocular Irritation

Three artificial tear solutions, one containing HEC and one containing HPMC, were tested for dispersion action using 10 subjects. Sterilized fluorescein was added to a final 2% concentration in each solution. Corneal and aqueous humor fluorescein contents were measured with a slit lamp fluorophotometer. Four drops of each tear solution, given 5 min apart, were instilled into the conjunctival sac. Observations were made 1, 2, and 3 h later. Volunteers received at least two of the tear solutions throughout the experiment, with instillations spaced several days apart. The tear solution containing HEC gave higher values of fluorescein uptake by the stroma and anterior chamber than either of the other solutions. The HEC solution was a 30% more effective delivery system (of fluorescein). No signs of irritation were reported in this study.[47]

An eye lotion containing 0.5% CG produced no irritation when used on the eye.[214]

Dermal Irritation and Sensitization

A repeated insult patch test (RIPT) was used to evaluate the irritation and sensitization of 100 and 5% HEC. Patches were applied to the skin of 50 subjects for 24 h every other day for a total of 10 applications. Following a 2-week nontreatment period, challenge patches were applied to adjacent skin sites. All subjects had a score of 0, indicating that 100 and 5% HEC produced no irritation or sensitization[215] (Table 7).

Cosmetic products containing 0.3–1.0% HEC were evaluated by RIPTs in a total of 708 subjects. These products were nonirritating to mildly irritating and nonsensitizing. Similarly, in 21-day cumulative irritancy assays, products containing 0.3–0.5% HEC were essentially nonirritating in a total of 52 subjects. Results of individual studies are presented in Table 7.

Faucher et al.[216] conducted a comparison test of the anti-irritancy effects of HEC and Polymer JR, an ionic version of HEC. Aqueous solutions containing 2% of these compounds were applied to the forearm skin on 10 subjects and allowed to dry. Sodium lauryl sulfate (SLS) was subsequently applied to the same area under occlusive patches for 1 h. A control group, which was not administered either polymer, was treated with SLS. This procedure was repeated daily for 5 days and scoring was made 3 days later. HEC produced some anti-irritant effects, although Polymer JR clearly had a more potent effect. The average scores (max = 4) of SLS skin irritation were 3.6, 2.4, and 1.4 for the controls, 2% HEC, and 2% Polymer JR solutions, respectively. The investigators considered that these anti-irritancy effects were due to the blocking of skin-reactive sites.

An aqueous solution of 10% HPC was evaluated for irritation and sensitization in an RIPT. A series of occlusive patches was applied for 24 h to the same site on each of 50 subjects every other day for a total of 10 exposures. Following a 2-week nontreatment period, challenge patches were applied to adjacent sites. No reactions were observed; all scores were 0[217] (Table 7).

Various cosmetic products containing 0.7–0.8% HPC have been evaluated for irritation and sensitization by single insult patch test (SIPT), RIPT, and 21-day cumulative irritancy assays in a total of 7, 340, and 27 subjects, respectively.* These products were essentially nonirritating and nonsensitizing. Results of individual tests are presented in Table 7.

Skin tests of MC in 100 men and 100 women were negative for irritation[213] (Table 7).

Cosmetic products containing MC at concentrations of 0.2 and 0.25% were evaluated for dermal effects in a controlled use study and an RIPT, respectively. In the controlled use study conducted on a night cream containing 0.2% MC, the potential for irritation was no different from a similar control product in the 101 subjects tested.[218] A shampoo containing 0.25% MC was tested as a 10% dilution by RIPT in 50 subjects. No reactions were observed at induction or challenge with semi-occlusive patches of the product. Under occlusive conditions, reactions indicative of primary irritation were observed in 11 subjects at induction and in 6 subjects at challenge. The investigators concluded that the sample

*These totals may not reflect the actual number of subjects tested as some may have participated in more than one study.

was capable of inducing irritation and that the reactions at challenge were also those typical of irritation and not sensitization[219] (Table 7).

A facial cleanser containing 1.1% HPMC was evaluated for dermal irritation in a controlled use study. Twenty-five women used the product daily for 14 days; the majority did not have signs of irritation, and no signs of sensitization were observed. A few of the irritant reactions were due to the drying effect of the product[220] (Table 7).

CG was evaluated by patch tests on 200 human subjects; it was neither a primary dermal irritant nor a sensitizer[1] (Table 7).

CG was evaluated for irritation and sensitization in an SIPT with a challenge. CG (100%) was applied under a lintine disc for 5 days to each of 100 male and 100 female subjects. Three weeks later, a repeat application was made for 48 h. No reactions were observed after either application of CG[221] (Table 7).

A standard patch test was conducted to evaluate the dermal irritation of 7 urostomal adhesive discs, 1 of which was composed of CG, pectin, and gelatin. Each disc was applied to the back of each of 74 subjects and allowed to remain in place for 48 h. All testing was done in duplicate. Observations were made 1 and 24 h after disc removal; sites were scored on a scale of 0 to 3. The disc containing CG was significantly less irritating than the other 6 tested, giving mean scores of 0.03 and 0.04 at 1 and 24 h, respectively[222] (Table 7).

Various cosmetic products containing 0.2–3.0% CG or CMC have been evaluated for irritation and sensitization by SIPT, RIPT, and 21-day cumulative irritancy assays in a total of 158, 1526, and over 45 subjects, respectively.* These products were nonirritating to slightly irritating and nonsensitizing (Table 7).

Photosensitization

A modified Draize-Shelanski RIPT was used to evaluate the photosensitivity of a mascara containing 0.4% HEC. A panel of 101 subjects completed the test, half of whom were classified as having sensitive skin. Occlusive 24-h patches were applied to different quadrants of the back on each subject on Mondays, Wednesdays, and Fridays for a total of 10 insults. Two weeks later, a 48-h challenge patch was applied to an adjacent site. Sites were irradiated with UVA immediately after scoring of the first, fourth, seventh, tenth, and challenge patches. The UVA light source (~360 nm) was a Hanovia Tanette Mark I Lamp placed at a distance of 12 inches from the skin for 1 min. Sites were scored 48 h after each UVA exposure. No reactions were observed in any of the subjects[229] (Table 8).

A conditioning polish remover containing 0.7% HPC and a moisturizer containing 0.25% CG were evaluated for photosensitivity in 101 and 105 subjects, respectively. Each subject received an occlusive patch on the upper back and another open patch on the wrist for 48 h. Two weeks later these procedures were repeated. Upon removal of the latter occlusive patch, each skin site was irradiated for 1 min with a Hanovia Tanette Mark I lamp emitting UVA of wavelength 360 nm at a distance of 12 inches from the skin. Sites were scored 48 h

*These totals may not reflect the actual number of subjects tested as some may have participated in more than one study.

TABLE 7. Clinical Irritation and Sensitization

Compound tested	*Type of test*	*No. of humans*	*Results/comments*	*Reference*
HEC 100%	RIPT[a]	50	All subjects had score of 0; nonirritating and nonsensitizing	215
HEC 5%	RIPT	50	All subjects had score of 0; nonirritating and nonsensitizing	215
HEC 1% in hair cream rinse	RIPT with 5% aqueous dilution	54	Total of 35 scores of 1 and 7 scores of 2 (max = 5) during induction; 3 scores of 1 at challenge—2 at 24 h, 1 at 72 h; nonirritating and nonsensitizing	223
HEC 0.75% in hair conditioner	RIPT insult with 50% aqueous dilution, challenge with 25% aqueous dilution	99	Scattered scores of 1 and 1 score of 2 (max = 3) during induction; 3 reactions at challenge, but only 1 lasting until 48 h; this subject was rechallenged with 25 and 13% dilutions and open application—mild erythema was elicited by both dilutions, no response to open application; mildly irritating under occlusion and nonsensitizing	224
HEC 0.5% in hair conditioner	RIPT insult with 50% aqueous dilution, challenge with 25% aqueous dilution	99	Scattered scores of 1 and 4 scores of 2 (max = 3) during induction; 9 reactions at challenge, but only 3 lasting until 48 h; these 3 were rechallenged with 25 and 13% dilutions and open application—2 subjects reacted to both dilutions but only 1 lasted until 48 h, no response to the open application; mildly irritating and nonsensitizing	225
HEC 0.5% in detangling rinse	RIPT with 10% aqueous dilution	97	No reactions during induction or challenge; nonirritating and nonsensitizing	226
HEC 0.5% in mascara	21-day Cumulative Irritancy Assay	15	Total composite score of 20.0 (max = 630); essentially nonirritating	227
HEC 0.5% in mascara	21-day Cumulative Irritancy Assay	15	Total composite score of 14.0 (max = 630); essentially nonirritating	227
HEC 0.5% in mascara	Maximization test with SLS[b] pretreatment	25	All subjects had score of 0 at challenge; nonsensitizing	228
HEC 0.5% in mascara	Maximization test with SLS pretreatment	25	All subjects had score of 0 at challenge; nonsensitizing	228
HEC 0.4% in mascara	RIPT	202, half classified as having sensitive skin	Total of 21 scores of 1 and 1 score of 2 (max = 3) during induction; 3 scores of 1 at challenge, but cleared totally by 48 h	229
HEC 0.4% in mascara	21-day Cumulative Irritancy Assay	10	Total composite score of 32.73 (max = 630); essentially nonirritating	230

HEC 0.3% in moisturizing cream	RIPT	107	Four subjects reacted during induction phase: 2 with ±, 1 with score of 1, and 1 with score of 2+ (max = 4); this last subject showed no irritation when patched on an adjacent site; no reactions at challenge; nonsensitizing	231
HEC 0.3% in moisturizing lotion	21-day Cumulative Irritancy Assay	12	Total composite score of 48.3 (max = 630); essentially nonirritating	232
HEC 2% in aqueous solution	Anti-irritation test with subsequent treatment of SLS	10	HEC showed some anti-irritancy effects attributed to blocking of skin-reactive sites	216
HPC 10% in aqueous solution	RIPT	50	No reactions during induction of challenge; all subjects had score of 0; nonirritating and nonsensitizing	217
HPC 0.8% in antiperspirant	SIPT[c]	7	Slight erythema seen in 3 subjects; slight to distinct dryness in 5 subjects	233
HPC 0.8% in antiperspirant	RIPT	97	Minimal reactions noted on induction consisting of slight erythema and 1 erythema with edema—not considered significant; no reactions on challenge; nonirritating and nonsensitizing	234
HPC 0.8% in body cleanser	RIPT	91	Three subjects with doubtful erythema and one with erythema during induction; no reactions at challenge; nonirritating and nonsensitizing	235
HPC 0.7% in conditioning polish remover	RIPT (Schwartz-Peck Prophetic Patch)	101	No reactions were observed during induction or challenge; nonirritating and nonsensitizing	236
HPC 0.7% in conditioning polish remover	RIPT (Draize-Shelanski)	51	No reactions observed to open patches; three weak reactions noted during occlusive induction period; no reactions on challenge; essentially nonirritating and nonsensitizing	236
HPC 0.7% in conditioning polish remover	21-day Cumulative Irritancy Assay	27	Product gave a total score (based on 10 subjects) of 21.3 (max = 630); essentially nonirritating	237
MC 100%	Patch test (unspecified)	200	No signs of irritation	213
MC 0.2% in night cream	Controlled Use Study, 3 weeks	101	Three complaints of dryness; potential for producing adverse effects no different from control products	218
MC 0.25% in shampoo	RIPT tested as 10% dilution	50	No reactions under semi-occluded conditions; irritation seen in 11 subjects at induction and 6 at challenge under occlusive conditions; capable of inducing irritation but nonsensitizing	219

TABLE 7. (Continued)

Compound tested	*Type of test*	*No. of humans*	*Results/comments*	*Reference*
HPMC 1.1% in facial cleanser	Controlled Use Study, 2 weeks	25	Few irritant reactions noted; some due to drying effect of product; no signs of sensitization	220
CG 100%	Patch test (unspecified)	200	No primary dermal irritation; did not appear to be sensitizer	1
CG 100%	SIPT (5 days) with challenge	200	No reactions noted; nonirritating and nonsensitizing	221
CG in adhesive disc	SIPT	74	Significantly less irritating than other discs tested; mean irritation scores of 0.03 and 0.04 (max = 3) at 1 and 24 h, respectively	222
CG 3.0% in wrinkle-smoothing cream	SIPT	15	AII[d] = 0.17, reference AIIs of 0.17, 0.12; no significant difference in irritancy between test and controls	238
CG 3.0% in wrinkle-smoothing cream	RIPT	89	Barely perceptible irritation in 8 subjects, mild in 1, no reactions at challenge; essentially nonirritating and nonsensitizing	239
CG 1.6% in foundation	RIPT	87	Barely perceptible irritation in 12 subjects, mild in 9 at induction; 3 barely perceptible at challenge; nonsensitizing	240
CG 1.1% in product (not specified)	SIPT	19	AII = 0.08; comparable to reference control with AII = 0.10	241
CG 1.1% in medicated lotion	RIPT	86	Barely perceptible irritation in 3 subjects at induction; no reactions at challenge; nonirritating and nonsensitizing	242
CG 1.1% in medicated lotion	21-day Cumulative Irritancy Assay	Not specified	No significant difference between test product and competitive control	243
CG 1.0% in paste mask	SIPT	19	AII = 0.08; significantly milder than competitive control with AII = 0.65	244
CG 1.0% in paste mask	RIPT	97	Mild irritation in 1 subject at induction; no reactions at challenge; nonirritating and nonsensitizing	245
CG 0.5% in eyeliner	21-day Cumulative Irritancy Assay	17	Mean cumulative irritation score of 2.1 (based on 10 subjects) on scale with max = 630; essentially nonirritating	246
CG 0.5% in eyeliner	RIPT (Modified Draize-Shelanski)	209	No reactions at induction; 2 mild reactions at challenge—considered clinically insignificant; nonirritating and nonsensitizing	247

CG 0.3% in moisturizing cream	21-day Cumulative Irritancy Assay	11	Mean cumulative irritation score of 72 (based on 10 subjects) with max = 630; slightly irritating	248
CG 0.3% in moisturizer	RIPT (Shelanski-Jordan)	210	One subject had 2+ reactions (max = 4+) to two induction patches; another subject had 2+ reaction 78 h after the 2nd challenge; nonirritating and nonsensitizing	249
CG 0.25% in moisturizer	SIPT with challenge (Schwartz-Peck Prophetic)	105	One weak reaction at induction and no reactions at challenge under occlusive conditions; no reaction to open induction; nonirritating and nonsensitizing	250
CG 0.25% in moisturizer	RIPT (Draize-Shelanski)	49	Five subjects with single weak reactions at induction and one with weak reaction at challenge under occlusive conditions; no reactions to open induction; nonirritating and nonsensitizing	250
CG 0.25% in product (not specified)	Maximization test with SLS pretreatment	25	No reactions were noted; nonirritating and nonsensitizing	251
CG 0.2% in cleanser	21-day Cumulative Irritancy Assay	17	Mean cumulative irritation score of 3.5 (based on 10 subjects) with max = 630; essentially nonirritating	246
CG 0.2% in cleanser	RIPT (Modified Draize-Shelanski)	209	Two reactions during induction – 1 mild erythema and 1 intense erythema and edema; 12 reactions at challenge – 9 mild erythema and 3 intense erythema; these were attributed to irritation; product considered not a strong irritant and not a sensitizer	247
CG 0.2% in makeup	RIPT (Modified Draize-Shelanski)	209	Four reactions during induction – 1 mild erythema and 3 intense erythema; 1 mild reaction at challenge considered clinically insignificant; product considered not a strong irritant and not a sensitizer	247
CG 0.2% in makeup	RIPT	206	No hyperpigmentation or positive skin reactions at challenge; nonsensitizing	252
CMC 0.605% in eye product	Maximization test with SLS pretreatment	50	No reactions were noted; nonirritating and nonsensitizing	253

[a]RIPT, Repeated Insult Patch Test.
[b]SLS, Sodium lauryl sulfate.
[c]SIPT, Single Insult Patch Test.
[d]AII, Average Irritation Index (max = 4).

TABLE 8. Clinical Photosensitization of Cosmetic Products

Ingredient tested	*Type of test*	*No. of humans*	*Results/comments*	*Reference*
HEC 0.4% in mascara	RIPT[a] with UVA exposure	101, half classified as having sensitive skin	No reactions observed in any of the subjects; nonphotosensitizing	229
HPC 0.7% in conditioning polish remover	SIPT[b] with challenge and UVA exposure	101	No reactions observed; nonphotosensitizing	236
HPC 0.7% in conditioning polish remover	RIPT with UVA exposure	51	No reactions observed; nonphotosensitizing	236
CG 0.25% in moisturizer	SIPT with challenge and UVA exposure	105	One weak response; nonphotosensitizing	250
CG 0.25% in moisturizer	RIPT with UVA exposure	49	No reactions observed; nonphotosensitizing	250
CMC 0.605% in eye product	RIPT with maximization and UV exposure	50	No reactions observed; nonphotosensitizing	253

[a]RIPT, Repeated Insult Patch Test.
[b]SIPT, Single Insult Patch Test.

later; all readings were negative for the polish remover, and one weak response was seen with the moisturizer[236,250] (Table 8).

These same two products, the polish remover and the moisturizer, were further evaluated for photosensitivity in Draize-Shelanski RIPTs in 51 and 49 subjects, respectively. Each occlusively patched skin site was irradiated for 1 min after the first, fourth, seventh, and tenth insults, as well as after the challenge patch. The light source was a Hanovia Tanette Mark I lamp emitting UVA of wavelength 360 nm and held at a distance of 12 inches from the skin. Each site was scored 48 h after irradiation; all readings for both products were negative[236,250] (Table 8).

An eye product containing 0.605% CMC was evaluated for photosensitivity in a modified maximization test on 50 subjects. Each subject received 6 open patch inductions over a 3-week period, and an open challenge patch after a 5-day rest. Each site received SLS pretreatment and irradiation at the first, third, and fifth insults and the challenge. The light source was a Hanovia Tanette Mark I lamp held at a distance of 12 inches from the skin for 1 min. Sites were scored 48 h after each irradiation; no reactions were noted[253] (Table 8).

Mucous Membrane Irritation

HEC, HPC, MC, CG, and CMC are all used in tampons. Recently, MC and CMC have been implicated in the development of Toxic Shock Syndrome (TSS).[254] Tierno et al.[255] have suggested that the CMC in tampons, as it is degraded by enzymes in the vaginal cavity (beta-glucosidase and cellulase), may become an exogenous source of nutrients for pathogenic organisms.

Less adverse effects were produced by a suppository base composed of HPC and carbomer than a comparable base tested in the contact treatment of cervical cancer lesions. Suppositories were inserted twice weekly for a total of 1 to 14 times. Adverse effects were noted in 10/43 patients using the HPC base compared to 21/42 patients who used the other base. These effects ranged from vaginal and external genitalia erosion to micturition pain to headache, fever, and nausea.[256]

No evidence of irritation or other adverse effects were noted in the vaginal mucosa or external genitalia of 134 women treated for vaginal infections with 5 g of CG (per subject).[1]

Inhalation

No inhalation studies have been conducted; however, Clayton and Clayton[257] state that long-term exposure to the dust of cellulose ethers in manufacturing operations has not led to any known adverse effects.

SUMMARY

HEC, HPC, MC, HPMC, and CG are modified cellulose polymers derived from the reaction of the three free hydroxyl groups in the 2–, 3–, and 6– positions of the anhydroglucose unit of the cellulose molecule. The number of hydroxyl groups reacting, as well as the nature of the substituent group, largely determine the physical properties, particularly solubility, of the product. The viscosity of the final product is greatly affected by the molecular weight of the starting cellulose. All of these cellulose ethers are odorless, tasteless, and very stable chemically.

The cellulose derivatives are used in a wide variety of cosmetics and toiletries as thickeners, suspending agents, film formers, stabilizers, emulsifiers, emollients, binders, or water-retention agents. Generally, the majority of uses is in hair products, eye and facial makeups, and skin care preparations. The concentration of use can range up to 10%; however, the celluloses are most frequently used in concentrations of >0.1–1%. HEC, HPC, MC, HPMC, and CG were used in a total of 422, 82, 144, 197, and 812 formulations, respectively, in 1981.

The cellulose derivatives are used widely as an ingredient in pharmaceutical and industrial products. Additionally, all five derivatives are approved as Indirect Food Additives, and all but HEC are approved as Direct Food Additives. MC and CG are GRAS food substances.

The cellulose derivatives pass essentially unchanged through the gastrointestinal tract following oral administration to rats, dogs, and man. Rabbits apparently digest about 50% of an ingested amount of CG, although this has been attributed to bacterial action present only in herbivorous animals.

Acute toxicity studies indicate that the cellulose derivatives are practically nontoxic when administered by inhalation or by oral, intraperitoneal, subcutaneous, or dermal routes. Intravenous injections of HPC in mice and rats and CMC in dogs were nontoxic; however, iv injections of MC to dogs and rabbits produced hematological reactions, retention and accumulation of MC in the liver, spleen, lymph nodes, kidney, and vascular walls, and small atherosclerotic lesions of the aorta (in rabbits only).

Ocular and dermal irritation studies indicate 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 irritation was noted in the genital mucosae of rabbits treated topically with a moisturizing cream containing 0.3% CG.

Subchronic oral studies indicate that the cellulose derivatives are essentially nontoxic when administered to rats, chickens, dogs, and rabbits. Subchronic dermal studies also indicated that cosmetic products containing CG were nontoxic in rats.

Subchronic iv administration of up to 10.0% HEC to dogs produced marked anemia, leukopenia, and increased sedimentation rate and plasma viscosity at the low dose (high viscosity) and extensive atheromatous and fibrous lesions at the high dose (low viscosity). The high-dose group gave evidence of HEC storage by the presence of swollen hepatic, glomerular endothelial, and endocardial cells. Similar effects were noted in dogs given repeated iv injections of MC and CMC.

Chronic oral studies indicated that the cellulose derivatives were essentially nontoxic in rats, mice, dogs, and guinea pigs when administered for periods up to 2 years. Groups of animals receiving a diet of 20–30% cellulose did have some growth retardation and some deaths; however, these were attributed to the nonnutritive bulk content of the diet.

HPMC was nonsensitizing in guinea pigs at concentrations up to 25%, whereas cosmetic products containing HEC and CG were nonphototoxic in rabbits.

In a teratogenicity study in which pregnant mice were injected ip with 1 or 4% HEC, fetal resorption was significantly increased at both concentrations as compared with controls, and weights of surviving fetuses in the 4% HEC group were significantly increased. Other teratogenicity/reproduction studies in which the cellulose derivatives were administered orally to rats, rabbits, mice, and hamsters produced no significant teratogenic or reproductive effects.

MC, CMC, and CG were nonmutagenic in various tests both with and without metabolic activation. MC was also nontumorigenic when injected subcutaneously in black rats. When injected ip, MC significantly increased the percentage of tumor regressions in mice transplanted with Murphy-Sturm lymphosarcoma.

The World Health Organization has established an acceptable daily intake for man of up to 25 mg/kg body weight for HPC, HPMC, MC, and CG; this intake level represents the sum total of modified celluloses. Daily doses of up to 6 g MC for up to 240 days have been effective as a laxative and have produced no toxic effects in man. Similarly, large doses (2–18 g twice daily) of CG have been administered orally as a laxative for periods of up to 3 years with no adverse effects other than mild abdominal discomfort or diarrhea.

No ocular irritation was observed in a clinical evaluation of an eye product containing 0.5% CG.

The cellulose derivatives (concentrations of 5–100%) and products containing these derivatives were nonirritating to mildly irritating, nonsensitizing, and nonphotosensitizing when evaluated by clinical SIPTs, RIPTs, 21-day cumulative irritancy assays, and controlled use studies.

The use of MC and CMC in tampons has recently been implicated in the development of Toxic Shock Syndrome. CMC appears to be an exogenous source of nutrients for pathogenic organisms as a result of enzymic degradation in the vaginal cavity. Women treated for vaginal infections with CG had no evidence of vaginal irritation or other adverse effects.

No clinical inhalation studies have been conducted; however, long-term exposure to the dust of cellulose ethers in manufacturing operations has not led to any known adverse effects.

CONCLUSION

On the basis of the available animal and clinical data presented in this report, the Expert Panel concludes that Hydroxyethylcellulose, Hydroxypropylcellulose, Methylcellulose, Hydroxypropyl Methylcellulose, and Cellulose Gum are safe as cosmetic ingredients in the present practices of use and concentration.

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