Toxicological profile for

Cellulose acetate

This ingredient has been assessed to determine potential human health effects for the consumer. It was considered not to increase the inherent toxicity of the product and thus is acceptable under conditions of intended use.

1. Name of substance and physico-chemical properties

1.1. IUPAC systematic name

[(2R,3S,4S,5R,6R)-5-Acetyloxy-3,4,6-trihydroxyoxan-2-yl]methyl acetate (PubChem)

1.2. Synonyms

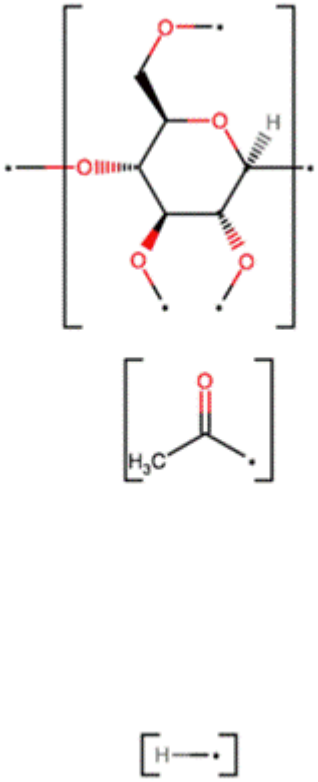
Cellulose acetate; EASTMAN cellulose acetate CA 398-10NF; A 432-130B; Acetate cotton; Acetate ester of cellulose; Acetic acid, cellulose ester; Acetose; Acetyl 35; Acetylcellulose; Allogel; Ampacet C/A; Bioden; Ca (cellulose acetate); Cellidor; Cellidor A; Cellit K 700; Cellit L 700; Cellulose 2,5-acetate; Cellulose monoacetate; Cellulose, 2,5-diacetate; Cellulose, acetate; Cellulose, diacetate; Cellulose, triacetate; Crellate; DP 02; DP 06; Duoflux; E 376-40; E 383-40; E 394-30; E 394-40; E 394-45; E 394-60; E 398-10; E-400-25; Eastman 298-10; Etrol OEM; HSDB 964; Monoacetylcellulose; Nicollembal; Nixon C/A; PP 612; PP 613; PP 628; Plastacele; Stripmix; Strux; Tenite I; UNII-3J2P07GVB6; Vladipor; t-Cellit; YM 10; Tenite acetate 105MS (ChemIDplus)

1.3. Molecular formula

C2 H4 O2.x-Unspecified (ChemIDplus)

1.4. Structural Formula

(ChemIDplus)



1.5. Molecular weight (g/mol)

minimum 28,000 (US EPA, 1995)

1.6. CAS registration number

9004-35-7

1.7. Properties

1.7.1. Melting point

(°C): Approx 260 (PubChem); 230-250 (Ash & Ash, 2004)

1.7.2. Boiling point

(°C): Not applicable.

1.7.3. Solubility

Almost insoluble in water.

1.7.4. pKa

No data available to us at this time.

1.7.5. Flashpoint

(°C): >300

1.7.6. Flammability limits (vol/vol%)

Flammable, not self-extinguishing, moderate fire risk (PubChem).

1.7.7. (Auto)ignition temperature

(°C): No data available to us at this time.

1.7.8. Decomposition temperature

(°C): 304 (Ash & Ash, 2004)

1.7.9. Stability

Stable at normal temperatures and pressure.

1.7.10. Vapor pressure

Not applicable

1.7.11. log Kow

-2 (estimated) (PubChem)

2. General information

2.1. Exposure

Probable Routes of Human Exposure:

Dry-spinning is simpler operation & gives greater production but solvents evaporated in dry-spinning must be exhaust ventilated to avoid risk of fire & explosion & possible health

hazard to workers because of their toxic nature. /artificial fibers/ [International Labour Office. Encyclopedia of Occupational Health and Safety. Volumes I and II. New York: McGraw-Hill Book Co., 1971., p. 526] **PEER REVIEWED**

As taken from HSDB, 2002

Industrial processes with risk of exposure: leather tanning and processing; paintings (pigments, binders and biocides); plastic composites manufacturing; sewer and wastewater treatment; textiles (printing, dyeing, or finishing). Activities with risk of exposure: preparing and mounting animal skins (taxidermy).

As taken from HazMap, 2020

Uses:

Excipient for pharmaceuticals, enteric coatings, in coatings for leather, paper, glass, plastic, wire screen and electrical wiring, in adhesives, paint removers, as barrier and release coatings for pressure-sensitive tape, in food contact materials, paper, paperboard, waterproofing and sizing of textiles, photographic film and in closures for sealing gaskets for food containers (Ash M and Ash I, 2004).

Cellulose acetate is reported to be used in cosmetics at concentrations of 0.01-5% with the highest levels found in foundations and suntan preparations (CIR, 2009).

Used as a film-forming agent in cosmetics in the EU. As taken from CosIng (Cosmetic substances and ingredients database). Available at https://ec.europa.eu/growth/tools-databases/cosing/, accessed April 2020.

“Cellulose acetate (CA) has been a material of choice for spectrum of utilities across different domains ranging from high absorbing diapers to membrane filters. Electrospinning has conferred a whole new perspective to polymeric materials including CA in the context of multifarious applications across myriad of niches. In the present review, we try to bring out the recent trend (focused over last five years' progress) of research on electrospun CA fibers of nanoscale regime in the context of developmental strategies of their blends and nanocomposites for advanced applications. In the realm of biotechnology, electrospun CA fibers have found applications in biomolecule immobilization, tissue engineering, bio-sensing, nutraceutical delivery, bioseparation, crop protection, bioremediation and in the development of anti-counterfeiting and pH sensitive material, photocatalytic self-cleaning textile, temperature-adaptable fabric, and antimicrobial mats, amongst others. The present review discusses these diverse applications of electrospun CA nanofibers.” As taken from Konwarh R et al. 2013. Biotechnol. Adv. 31(4), 421-37. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/23318668

“Cellulose plastic materials are used extensively in display packaging, irrigation pipe, frames for eyeglasses, and in rayon and acetate textiles.”

As taken from Wilson and McCormick, 1955. Ind. Med. Surg. 24, 491-496.

National Occupational Exposure Survey (1981 - 1983)
Estimated Numbers of Employees Potentially Exposed to Cellulose Acetate (CAS RN 9004-35-7) by Occupation*

Code	Occupation Description (1980)	Total # Employees (Male & Female)	Total # Female Employees

019	MANAGERS AND ADMINISTRATORS, N.E.C.	130	130
073	CHEMISTS, EXCEPT BIOCHEMISTS	1,690	682
075	GEOLOGISTS AND GEODESISTS	28	
083	MEDICAL SCIENTISTS	63	49
095	REGISTERED NURSES	30,741	22,212
096	PHARMACISTS	111	47
103	PHYSICAL THERAPISTS	210	180
188	PAINTERS, SCULPTORS, CRAFT-ARTISTS, AND ARTIST PRINTMAKERS	108	72
203	CLINICAL LABORATORY TECHNOLOGISTS AND TECHNICIANS	1,596	336
207	LICENSED PRACTICAL NURSES	3,727	3,680
213	ELECTRICAL AND ELECTRONIC TECHNICIANS	18	
308	COMPUTER OPERATORS	2,260	282
335	FILE CLERKS	331	
426	GUARDS AND POLICE, EXC. PUBLIC SERVICE	32	
446	HEALTH AIDES, EXCEPT NURSING	780	514
447	NURSING AIDES, ORDERLIES, AND ATTENDANTS	1,773	1,624
453	JANITORS AND CLEANERS	843	36
515	AIRCRAFT MECHANICS, EXC. ENGINE	76	
547	SPECIFIED MECHANICS AND REPAIRERS, N.E.C.	365	28
575	ELECTRICIANS	263	
633	SUPERVISORS, PRODUCTION OCCUPATIONS	188	28
637	MACHINISTS	2,156	431
706	PUNCHING AND STAMPING PRESS MACHINE OPERATORS	32	
709	GRINDING, ABRADING, BUFFING, AND POLISHING MACHINE OPERATORS	251	100
719	MOLDING AND CASTING MACHINE OPERATORS	2,234	1,685
735	PHOTOENGRAVERS AND LITHOGRAPHERS	50	4
736	TYPESETTERS AND COMPOSITORS	6,095	1,292
737	MISCELLANEOUS PRINTING MACHINE OPERATORS	271	36
743	TEXTILE CUTTING MACHINE OPERATORS	97	32
744	TEXTILE SEWING MACHINE OPERATORS	4,063	4,063
756	MIXING AND BLENDING MACHINE OPERATORS	781	
759	PAINTING AND PAINT SPRAYING MACHINE OPERATORS	257	43
769	SLICING AND CUTTING MACHINE OPERATORS	13,049	5,176
774	PHOTOGRAPHIC PROCESS MACHINE OPERATORS	63	16
777	MISCELLANEOUS MACHINE OPERATORS, N.E.C.	1,373	619
785	ASSEMBLERS	5,465	3,628
796	PRODUCTION INSPECTORS, CHECKERS, AND EXAMINERS	86	13
859	MISCELLANEOUS MATERIAL MOVING EQUIPMENT OPERATORS	263	148
888	HAND PACKERS AND PACKAGERS	97	97
889	LABORERS, EXCEPT CONSTRUCTION	1,493	
TOTAL		83,508	47,285

*(1) The estimates for each occupation apply across the surveyed industries in which the agent was observed. Not all industries were surveyed, and not all agents were observed in all surveyed industries. (2) When using the estimates, standard errors associated with estimates should be considered. (3) Potential exposures to a chemical agent are categorized as actual (i.e., the surveyor observed the use of the specific agent) or

tradename (i.e., the surveyor observed the use of a tradename product known to contain the specific agent). The estimates presented in the table combine both categories.

As taken from NIOSH, available at https://web.archive.org/web/20111028115705/http://www.cdc.gov/noes/noes2/x6205occ.html

2.2. Combustion products

No data available to us at this time.

2.3. Ingredient(s) from which it originates

HYDROLYSIS OF CELLULOSE TRIACETATE IN AQUEOUS ACETIC ACID USING A SULFURIC ACID CATALYST [SRI] **PEER REVIEWED**

Reacting cellulose (wood pulp or cotton linters) with acetic acid or acetic anhydride, with sulfuric acid catalyst. The cellulose is fully acetylated (three acetate groups per glucose unit) and at the same time the sulfuric acid causes appreciable degradation of the cellulose polymer so that the product contains only 200-300 glucose units per polymer chain. [Lewis, R.J., Sr (Ed.). Hawley's Condensed Chemical Dictionary. 13th ed. New York, NY: John Wiley & Sons, Inc. 1997., p. 228] **PEER REVIEWED**

Cellulose acetates obtained by treating cellulose with acetic anhydride at various temps for different lengths of time to produce amorphous white solid material in granular, flake, or powder form from which fibers may be formed by extrusion. [Budavari, S. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 1996., p. 2018] **PEER REVIEWED**

As taken from HSDB, 2002

3. Status in legislation and other official guidance

FIFRA Requirements:

Cellulose acetate is exempted from the requirement of a tolerance when used as a pesticide rate-release regulating agent in accordance with good agricultural practice as inert

(or occasionally active) ingredients in pesticide formulations applied to growing crops only. [40 CFR 180.1001(d) (7/1/2000)] **PEER REVIEWED**

As taken from HSDB, 2002

Cellulose acetate can be used as an inert ingredient in pesticide products that are exempt from Federal regulation under the Minimum Risk Exemption regulations in 40 CFR 152.25(f) (US EPA 2020). It is also listed in the US EPA InertFinder Database (2020) as approved for food and non-food use pesticide products. For food use, it is regulated under 40 CFR Part 180.950e (Tolerances and Exemptions for Pesticide Chemical Residues in Food. Tolerance exemptions for minimal risk active and inert ingredients) (US EPA, 2020).

Cellulose acetate is included on the FDA's list of Substances Added to Food (formerly EAFUS) as an emulsifier or emulsifier salt and a stabilizer or thickener, and is covered under 21 CFR sections 175.300 (Resinous and polymeric coatings) and 182.90 (Substances migrating to food from paper and paperboard products) (FDA, 2020a,b).

Cellulose, acetate is pre-registered under REACH ("envisaged registration deadline 31 May 2018") (ECHA).

Cellulose, acetate (CAS RN 9004-35-7) is not classified for packaging and labelling under Regulation (EC) No. 1272/2008 (ECHA, 2020).

Cellulose acetate (CAS RN 9004-35-7) is listed in the US EPA Toxic Substances Control Act (TSCA) inventory and is exempt from reporting under TSCA CDR (Chemical Data Reporting Rule). The Chemical Data Reporting (CDR) Rule requires companies that manufacture (including import) certain chemicals at certain volumes in the U.S. to report to EPA every four years through its CDR.

The TSCA inventory and 2020 CDR Full Exempt list are available at https://iaspub.epa.gov/sor_internet/registry/substreg/searchandretrieve/searchbylist/search.do

Cellulose acetate (CAS RN 9004-35-7), cellulose acetate CA-320S and cellulose acetate CA-398-10 (no CAS RNs given) are included on the US FDA's list of inactive ingredients for approved drug products. They are permitted for use as ingredients in various products, at the following maximum potencies per unit dose:

Inactive Ingredient	**Route**	**Dosage Form**	**CAS Number**	**UNII**	**Maximum Potency per unit dose**
CELLULOSE ACETATE	ORAL	CAPSULE	9004357	3J2P07GVB6	22.15mg
CELLULOSE ACETATE	ORAL	TABLET	9004357	3J2P07GVB6	27.39mg
CELLULOSE ACETATE	ORAL	TABLET, CHEWABLE	9004357	3J2P07GVB6	6.86mg

CELLULOSE ACETATE	ORAL	TABLET, EXTENDED RELEASE	9004357	3J2P07GVB6	50.16mg
CELLULOSE ACETATE	ORAL	TABLET, FILM COATED, EXTENDED RELEASE	9004357	3J2P07GVB6	44.6mg
CELLULOSE ACETATE CA-320S	ORAL	TABLET, EXTENDED RELEASE		NA	36.02mg
CELLULOSE ACETATE CA-398-10	ORAL	TABLET		NA	20.93mg
CELLULOSE ACETATE CA-398-10	ORAL	TABLET, EXTENDED RELEASE		NA	47.49mg

As taken from FDA, 2020c

Cellulose acetate (CAS RN 9004-35-7) has been “identified as low concern to human health by application of expert validated rules” and is “not considered to pose an unreasonable risk to the health of workers and public health on the basis of the Tier I IMAP assessment” (NICNAS, 2018).

Cellulose, acetate (CAS RN 9004-35-7) is included on the New Zealand Inventory of Chemicals and may be used as a single component chemical under an appropriate group standard (NZ EPA, 2006).

4. Metabolism/Pharmacokinetics

4.1. Metabolism/metabolites

No data available to us at this time.

4.2. Absorption, distribution and excretion

“The minimum number average molecular weight of cellulose acetate is 28,000. Substances with molecular weights greater than 400 generally are not absorbed through the intact skin, and substances with molecular weights greater than 1,000 generally are not absorbed

through the intact gastrointestinal tract. Chemicals not absorbed through skin or GI tract generally are incapable of eliciting a toxic response." As taken from US EPA. 1995. Federal Register 60(163), 43738 available at https://www.gpo.gov/fdsys/pkg/FR-1995-08-23/pdf/95-20889.pdf

4.3. Interactions

No data available to us at this time.

5. Toxicity

5.1. Single dose toxicity

Range of Toxicity:

These agents are considered not to be a toxic hazard in the quantities available through normal exposure or package size. [Rumack BH POISINDEX(R) Information System Micromedex, Inc., Englewood, CO**,** 2009**;** CCIS Volume 142, edition expires Nov, 2009. Hall AH & Rumack BH (Eds): TOMES(R) Information System Micromedex, Inc., Englewood, CO, 2009; CCIS Volume 142, edition expires Nov, 2009.] **PEER REVIEWED**

As taken from HSDB, 2002

5.2. Repeated dose toxicity

Subchronic Oral Toxicity of Cellulose Acetate in Rats (Abstract). The potential of cellulose-acetate (9004-35-7) to produce adverse effects was evaluated in CD-Sprague-Dawley-rats. Rats were fed concentrations of cellulose-acetate in their diets equivalent to 500, 2500, or 5000mg/kg for 94 to 96 consecutive days. No mortality or compound related toxicity was observed. Autopsies were conducted at week 13. The results of physical observations, ophthalmology, body weight, food consumption, hematology, clinical chemistry, organ to body weight ratios, gross pathology and histopathology revealed no evidence of an adverse effect related to treatment with cellulose-acetate**.** As in other studies of cellulose derivatives, the only consistent effect of very high doses in the feed appeared to be a reduction in the nutritional value of the feed which was manifested as a decrease in

body weight gain or an increase in food consumption. The authors conclude that cellulose-acetate is nontoxic in rats at doses up to 5000mg/kg/day or an equivalent concentration of 7.2 to 10.0% of the diet . As taken from Thomas WC et al. Food and Chemical Toxicology, 1991, Vol. 29, No. 7, pages 453-458. PubMed, 2009 available at http://www.ncbi.nlm.nih.gov/pubmed/1894211?dopt=Abstract

Human Toxicity Excerpts:

TOXICITY IS NOT ASSOC WITH THESE POLYMERS. SYNTHETIC PROCESS MAY INVOLVE EXPOSURE TO SOLVENTS & ORG ACID COMPD WHICH MAY RESULT IN SKIN REACTIONS. /CELLULOSICS/ [Hamilton, A., and H. L. Hardy. Industrial Toxicology. 3rd ed. Acton, Mass.: Publishing Sciences Group, Inc., 1974., p. 337] **PEER REVIEWED**

As taken from HSDB, 2002

5.3. Reproduction toxicity

Species	Test conditions	Effects	Reference
Rat, white (11 treated, 19 control females)	Early Soviet paper, translated for the US Environmental Protection Agency. Throughout pregnancy, animals were given an aqueous extract of a cellulose acetate film treated with formamide. Animals killed on the 19th day of pregnancy and embryos examined. An inadequate and poorly described study. The dose was not specified, nor was the exposure route (possibly the extract was given as a drinking water substitute). No further details available.	Reported increase in embryonic death, especially preimplantation, and reduced foetal length. This was a test on extractable material rather than on cellulose acetate molecule itself, and the chemicals potentially responsible for the reported effects were not identified.	Shtannikov et al. 1972.

5.4. Mutagenicity

In vivo				
Species	**Test conditions**	**Endpoint**	**Result**	**Reference**
Mouse, NMRI (3 males per group)	A comet assay study of compounds' ability to inhibit DNA damage caused by subsequent exposure to tobacco smoke.	DNA damage	-ve The use of cellulose acetate as a vehicle	Villard et al. 1998.

	Test chemicals were given, by gavage, in a vehicle (0.5% aqueous cellulose acetate). A control group received the vehicle only (equivalent to a cellulose acetate dose of 50 mg/kg bw) daily for 8 days. 45 min after each dose, the animals were exposed for 10 min to either fresh air or cigarette smoke. DNA damage was assessed in the lymphocytes, liver and lung. There was no untreated control group.		suggests it was without effect.	
Rat, white, numbers unspecified	Early Soviet paper translated for the US Environmental Protection Agency. Bone marrow mitotic index was measured in rats given brief access to diet containing 1% of two cellulose acetate polymers. No further details were available. Study is irrelevant but is included here because the investigators claimed (incorrectly) that a change in mitotic index was an indication of mutation.	None	Not relevant Mitotic index was not affected but this is not relevant to genotoxicity	Shtannikov et al. 1972.
Drosophila melanogaster	Early Soviet paper, translated for the US Environmental Protection Agency. Aqueous extracts of two cellulose acetate film samples (described as treated with formamide or pyridine) were added to the feed at concentrations of 0.8, 4 and 20%. Treated males and females were mated, the offspring raised on untreated nutrient and cross-bred to produce a third generation. Offspring were assessed for mutations (white eye mutants and sex-linked recessive lethal [SLRL] mutations, indicated by reduced viability). The study explored the toxicity of extractable material (not further specified) rather than the cellulose acetate polymer molecule itself. A poorly described study.	Mutation	? No effect on eye colour mutation rate. Dose-related decreases in offspring viability, possible effect on SLRL rate, in third generation. The extracted chemicals responsible were not identified.	Shtannikov et al. 1972.
+ve, positive; -ve, negative; ?, equivocal; with, with metabolic activation; without, without metabolic activation				

5.5. Cytotoxicity

“REACTION OF VAGINAL TISSUE OF RABBITS TO INSERTED SPONGES MADE OF ACETYLCELLULOSE. VAGINAL WALL & ITS MUCOSAL LINING SHOWED SIGNS OF CYTOTOXICITY, EXTRACTS OF SPONGES TESTED FOR CYTOTOXICITY SHOWED SIGNIFICANT INHIBITION OF (3)H-THYMIDINE UPTAKE. [CHVAPIL M ET AL; J BIOMED MATER RES 13 (1): 1-13 (1979)] **PEER REVIEWED.”

As taken from HSDB, 2002

“Based on accumulating evidence that the 3D topography and the chemical features of a growth surface influence neuronal differentiation, we combined these two features by evaluating the cytotoxicity, proliferation, and differentiation of the rat PC12 line and human neural stem cells (hNSCs) on chitosan (CS), cellulose acetate (CA), and polyethersulfone (PES)-derived electrospun nanofibers that had similar diameters, centered in the 200-500 nm range. None of the nanofibrous materials were cytotoxic compared to 2D (e.g., flat surface) controls; however, proliferation generally was inhibited on the nanofibrous scaffolds although to a lesser extent on the polysaccharide-derived materials compared to PES....” As taken from Du J et al. 2014. Carbohydr. Polym. 99, 483-90. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/24274534?dopt=AbstractPlus

5.6. Carcinogenicity

Species	**Test conditions**	**Evidence of carcinogenicity**	**Reference**
Humans (approximately 9000 men)	A prospective cohort study of men employed at a chemical plant in Tennessee manufacturing chemicals, fibres and plastics. Workers employed on 31st December 1971 were followed until 1982 and the cancer mortality rates were compared with those for the general population of Tennessee state, the United States, and a group of non-exposed employees from the same company. The mean and median lengths of employment for the cohort were 24.8 and 22 years respectively. Workers employed in the acetate yarn, cellulose esters, filter products and tenite plastics divisions were exposed to cellulose acetate amongst other chemicals; the primary exposures in the tenite plastics division being	None Total number of cancer deaths (176) was lower than that predicted from the general state (227) and national population (224), and similar to that expected for non-exposed workers (179). No specific cancer type was increased. Lung/respiratory cancer deaths (63) were significantly lower than would be expected based on state (94.3) and national (88.0) rates, and not significantly higher than expected based on non-exposed employees (51.6). Similar results were reported for a subcohort of workers employed for at least 20 years at the start of the study. Analysis by work division found similar decreases in all cancer and lung cancer mortality rates amongst subcohorts working with acetate yarn, cellulose esters, filter products and	Pifer et al. 1986.

	to cellulose esters and plasticizers.	tenite plastics (when compared with state rates).	
Human (7,487 men and 2,724 women)	A retrospective cohort study of workers employed in a Quebec plant producing fibres made from extruding cellulose acetate and manufactured textiles from these fibres. Workers employed at the plant for at least 1 year and either working on 1 January 1947 or employed between 1 January 1947 and 31 December 1977, were followed until 31 December 1986. Standard mortality rates (SMRs) were calculated (for "inception" and "prevalent" subcohorts, as well as combined) based on the entire province of Quebec. Mean length of employment was 12.5 years for males and 6.3 years for females. No data on exposure levels were given, although workers in the cellulose acetate fibre manufacturing unit were mainly exposed to acetone, cellulose acetate dust, pyrolysis fumes from cellulose acetate and noise.	No clear evidence SMR for reticulum cell sarcoma was significantly increased (SMR 2.82, 95% CI 1.03-6.13) for men in the prevalent subcohort only. There were small, non-significant increases in deaths from malignant melanoma, reticulum cell sarcoma, multiple myeloma and leukaemias in men, and rectal cancer, breast cancer and leukaemias in women, but these were based on small numbers (1-8). Risk of dying from "any cancer" (RR 1.32, 95% CI 1.03-1.67) or non-Hodgkin's lymphomas (RR 4.28, 95% CI 1.18-14.89; 6 cases) were increased in those who had ever worked in the cellulose acetate fibre manufacturing unit. Non-significant increases in risk of death were found for reticulum cell sarcoma and liver and gallbladder cancer but the actual numbers were small (3-4). There was no association between cancer and duration of employment.	Goldberg & Thériault, 1994a.
Human (7,487 men and 2,724 women)	A standard mortality and nested case-control analyses of colorectal cancer amongst the cohort of synthetic textiles workers described above. The status of the workers was ascertained from January 1 1947 until December 31 1986 and the number of deaths from colorectal cancer compared with the mortality rates for the province of Quebec. In the case-control analyses, the incidence of, and mortality from, colon tumours, rectal cancers and combined colorectal cancers (at any age) amongst the cohort were assessed. Each case was matched and compared with 5 controls selected from the cohort. 91 cases of colorectal cancer were identified amongst the males and 18 cases amongst the females. 18 cases occurred in	Some, not convincing, evidence for a possible association with work in the cellulose acetate fibre manufacturing unit. In the whole cohort, there was no increase in SMR in men (0.69, 95% CI 0.52-0.92, 50 deaths) or women (1.02, 95% CI 0.57-1.69, 15 deaths). For men, the relative risk tended to increase with length of employment. A non-significant increase in risk of mortality from colorectal cancer was reported for men (RR 1.83, 95% CI 0.87-3.57) and women (RR 2.92, 95% CI 0.52-10.81) ever employed in the cellulose acetate fibre manufacturing unit when compared with all other processing units combined, but risk was not related to duration of employment. In the case-control analyses, RRs for the cellulose acetate unit (using 10-yr lag models) for each length of duration	Goldberg & Thériault, 1994b.

	males employed in the cellulose acetate manufacturing unit	category were above unity, but not to a statistically significant degree.	

“Foreign-body (FB) carcinogenesis is a classic model of multistage tumour development in rodents. Previous studies have demonstrated that the physical characteristics of the implant, and not the chemical composition, are the critical determinants of tumour development. The recent controversy over silicone breast implants has raised questions regarding the potential carcinogenicity of lifetime tissue exposure to silicone products. The present study was designed to determine whether the inflammatory and fibrotic reactions associated with silicone implants are due to a non-specific foreign-body reaction or whether these responses reflect the unique chemical composition of silicone. F344 rats were implanted subcutaneously with one of three biomaterials: silicone elastomer (Group 1); impermeable cellulose acetate filters (Group 2, positive control); or porous cellulose acetate filters (Group 3, negative control). “The silicone and cellulose implants of Groups 1 and 2 have been previously shown to induce fibrosarcomas in rodents, whereas the porous cellulose acetate implants of Group 3 have been shown to be non-carcinogenic. One week and two months after implantation, the pericapsular tissues were evaluated using histopathological and in situ immunohistochemical analyses. Endpoints included expression of leucocyte antigens CD4 (T helper/inducer), CD8 (T suppressor/cytotoxic) and CD11 b/c (macrophage), proliferating cell nuclear antigen (PCNA) as an indicator of proliferation, and in situ end-labelling (ISEL) of 3'OH DNA strand breaks as an indicator of DNA damage and apoptosis. The results indicated that the acute and chronic cellular responses to silicone (Group 1) were not different from impermeable cellulose filters (Group 2) of identical size and shape, suggesting that these responses were not unique to silicone. The inflammatory response to the carcinogenic cellulose and silicone implants (Groups 1 and 2) was attenuated and associated with the formation of a thick fibrotic capsule. In contrast, the porous cellulose filters (Group 3) induced a markedly different cellular response in which the inflammatory reaction was more extensive, prolonged and associated with minimal fibrosis. Within the fibrotic capsule surrounding the tumorigenic implants, but not the non-tumorigenic implants, cell proliferation and apoptotic cell death were increased and associated with persistent DNA strand breaks. Taken together, the results suggest that the micrometre-scale surface morphology of the implant determines the nature of the subsequent cellular response which may predispose to tumour development. Further, these studies serve to emphasize the critical importance of appropriate physical controls in studies designed to evaluate carcinogenic or autoimmune manifestations associated with silicone implants in order to rule out the contribution of the chronic foreign-body reaction”. As taken from James SJ et al. Biomaterials. 1997, May; 18(9):667-75. PubMed, 2009 available at http://www.ncbi.nlm.nih.gov/pubmed/9151998

5.7. Irritation/immunotoxicity

Effect of cellulose acetate materials on the oxidative burst of human neutrophils (Abstract). Following adverse clinical events involving seven patients undergoing renal dialysis using 12-year-old cellulose acetate hemodialyzers, this in vitro study was proposed in an effort to characterize the inflammatory response to the constituent cellulose acetate (CA) fiber

materials. Chemiluminescence (CL) and apoptosis assays were used to determine whether human neutrophils were activated by CA fiber materials and/or are sensitive to degradation/alteration of these fibers over time. Furthermore, the study examined in vitro assays with human neutrophils using a CA film, the solvents used in the film preparation and CA resin. The film could be cut to identical sized pieces in an effort to compare hemodialysis material effects in standardized amounts. For the CL assays, 60-min exposure was followed by secondary stimulation with n-formyl-met-leu-phe (fMLP) or phorbol-12-myristate-13-acetate (PMA). Short-term exposure (60-min postintroduction to CA materials) increased the inflammatory response as measured by the respiratory burst of neutrophils (p < or =.05), with CA fiber exposure significantly compared with cells alone. There was a trend toward an increased response with exposure to older fibers with secondary PMA stimulation. Apoptosis was increased 12% with exposure to the more aged fibers versus 2% with the new fibers. The fiber storage component, glycerol, significantly inhibited the oxidative response (p < or =.001; > or =80% suppression with concentrations of 5-20%). The solvents used in film preparation, N,N-dimethylacetamide and tetrahydrofuran, produced greater than a 70% and 60% suppression, respectively, of CL activity for all concentrations > or =1%. More work is needed to determine the specific nature of the interaction of inflammatory cells with CA materials, but early evidence suggests that neutrophils are activated by CA and display an altered response to more aged fibers. As taken from Moore MA et al. J Biomed Mater Res. 2001, Jun 5; 55(3):257-65. PubMed, 2009 available at http://www.ncbi.nlm.nih.gov/pubmed/11255178

“In September 1996, seven patients at Hospital A suffered conjunctivitis, hearing loss, diminished vision, and headaches 7-24 h after hemodialysis treatment. Eleven-year-old dialysis modules were identified as a common link between these patients. Degradation of the cellulose acetate (CA) material was identified as the cause of this incident. Degradation products were characterized from retrieved CA dialysis membranes. A series of synthesized CA degradation products was tested in vitro to assess toxicity. Based on the toxicity of the material preparations to the cells, animal tests were performed on selected CA degradation extracts and compared to extracts from actual dialysis membranes. Rabbits were IV-injected with extracts from a 13-year-old dialyzer, synthesized model compounds, and compared to controls. Ophthamological evaluation of the rabbits showed eye injury (iritis/ciliary flush) when the animals were treated with the old dialyzer or synthesized model compounds. Isolation and characterization of a toxic fraction from both of these extracts strongly indicated that oxidative stress at some point in the storage or manufacture of CA dialyzers created degradation products that reproduced some of the patient symptoms identified at Hospital A”. As taken from Lucas AD et al. J Biomed Mater Res. 2000, Sep; 53(5):449-56. PubMed, 2009 available at https://www.ncbi.nlm.nih.gov/pubmed/10984691

“Ulcerative colitis and Crohn's disease are the two most prevalent inflammatory bowel diseases. In both cases, the medically refractory and steroid-dependent type presents a therapeutic challenge. To help resolve this problem, a mainly Japanese team developed a new therapeutic option. There are two systems, both of which are able to selectively remove the main mediators of the disease, namely the activated pro-inflammatory cytokine-producing granulocytes and monocytes/macrophages, from the patient's blood circulation (GMA = granulocyte monocyte apheresis). One of the two systems is the Adacolumn((®)) (Immunoresearch Laboratories, Takasaki, Japan) consisting of the ADA-monitor and a single-use column, which contains approximately 35,000 cellulose acetate beads. The exact mode of action is not yet sufficiently understood, but however, a modulation of the immune system takes place. As a result, less pro-inflammatory cytokines are released. Furthermore,

the production of anti-inflammatory interleukin-1 receptor antagonist is increased, and the apoptosis of granulocytes boosted. The decreased LECAM-1-expression on leukocytes impedes the leukotaxis to the inflamed tissue, and CD10-negative immature granulocytes appear in the peripheral blood. Another effect to be mentioned is the removal of the peripheral dendritic cells and the leachate of regulatory T cells (T-regs). The second system is the Cellsorba((®)) FX Filter (Asahi Medical, Tokyo, Japan). The range of efficiency, the indication, and the procedure are very similar to the Adacolumn. Solely the additional removal of lymphocytes can possibly limit the implementation since lymphopenia can increase the risk of autoimmune disease. Both systems provide a low-risk therapy with few adverse reactions. ASFA recommendations for GMA in inflammatory bowel disease are 2B due to the fact that not enough randomized double-blind studies are available to proof the efficacy of this treatment". As taken from Leitner G et al. 2012. Trans. med. Hemother. 339, 246-252. PubMed, 2013 available at http://www.ncbi.nlm.nih.gov/pubmed/22969694

Sensitization

The literature contains a few papers reporting cases of allergic contact dermatitis provoked by spectacle frames containing cellulose acetate, or by a cellulose acetate membrane (Caravaca et al. 1987; Hausen & Jung, 1985; Kalensky & Jiraskova, 1980; Nakada & Maibach, 1998).

5.8. All other relevant types of toxicity

Cigarettes with defective filters marketed for 40 years: what Philip Morris never told smokers (Abstract).

"BACKGROUND: More than 90% of the cigarettes sold worldwide have a filter. Nearly all filters consist of a rod of numerous (> 12 000) plastic-like cellulose acetate fibres. During high speed cigarette manufacturing procedures, fragments of cellulose acetate that form the mouthpiece of a filter rod become separated from the filter at the end face. The cut surface of the filter of nearly all cigarettes has these fragments. In smoking a cigarette in the usual manner, some of these fragments are released during puffing. In addition to the cellulose acetate fragments, carbon particles are released also from some cigarette brands that have a charcoal filter. Cigarettes with filters that release cellulose acetate or carbon particles during normal smoking conditions are defective.

OBJECTIVE: Specific goals were to review systematically the writings of tobacco companies to: (a) identify papers that would document the existence of defective filters; (b) characterise the extent of the defect; (c) establish when the defect became known; (d) determine whether the defect exists on cigarettes marketed currently; (e) assess the prevalence of the defect on cigarettes manufactured by different companies; (f) define whether the knowledge of the defect had been withheld by the tobacco company as confidential and not disclosed publicly; and (g) ascertain the feasibility of correcting or preventing the defect.

METHODS: Document searches utilised databases of the scientific literature, medical journals, chemical abstracts, US Patents, Tobacco Abstracts, papers presented at tobacco

meetings and court documents. RESULTS: Sixty one documents of Philip Morris, Inc were selected for study because they disclosed specifically the "fall-out" of cellulose acetate filter fibres and, for cigarettes with charcoal filters, carbon particles from cigarette filters. The term "fall-out" was defined in 1985 laboratory protocols of Philip Morris, Inc. as "loose fibers (or particles) that are drawn out of the filter during puffing of the cigarette". As early as 1957, the health concern of inhaling cellulose acetate fibres released from cigarette filters was addressed by Philip Morris, Inc. A 1962 document reported the results of laboratory tests conducted by Phillip Morris, Inc that compared the "fall-out" of cellulose acetate fibres from the filters of their cigarettes (Marlboro) and cigarettes of their competitor (Liggett & Meyers). A 1997 overview by Phillip Morris of documents addressing the "fallout of carbon particles and cellulose acetate fibers from filters" stated that they were "essentially routine reports" of cigarette filter assays, and referenced a "Filter Fallout" memo written in 1961-more than 40 years ago. Most likely these tests are being conducted presently as illustrated by a 1999 report that details the revisions of the "fall-out" protocol of Phillip Morris, Inc and reports the results of tests that measured the discharge of cellulose acetate fibres and silica gel from beta cigarettes with a new type of filter. Our analysis of the "fall-out" tests results presented in the 61 "fall-out" documents showed that filter fibres and carbon particles were discharged from the filters of all types of cigarettes tested. These cigarette types (n = 130) included both coded cigarettes and popular brand name cigarettes. No publications were found in the scientific literature of the "fall-out" studies. Thus, the results of the "fall-out" studies are thought to have been withheld as confidential to Philip Morris, Inc. We have identified also other companies that have tested recently cigarettes for defective filters. In addition, our searches have shown that simple, expedient, and inexpensive technologies for decontaminating cigarette filters of loose cellulose acetate fibres and particles from the cut surface of the filter have been developed and described in 1997 and 1998 US patents. What is more important is that these patents also define methods for preventing or reducing the broken plastic-like fibres that arise during cigarette making. Many US patents (n = 607; 1957 to 2001) have been awarded for cigarette filters. Some of these inventions describe novel materials and unique filtration schemes that would eliminate or minimise the discharge of filter materials into mainstream smoke.

CONCLUSIONS: We have shown that: (a) the filter of today's cigarette is defective; (b) Philip Morris, Inc has known of this filter defect for more than 40 years; (c) the existence of this filter defect has been confirmed by others in independent studies; (d) many methods exist to prevent and correct the filter defect, but have not been implemented; and (e) results of investigations substantiating defective filters have been concealed from the smoker and the health community. The tobacco industry has been negligent in not performing toxicological examinations and other studies to assess the human health risks associated with regularly ingesting and inhaling non-degradable, toxin coated cellulose acetate fragments and carbon microparticles and possibly other components that are released from conventional cigarette filters during normal smoking. The rationale for harm assessment is supported by the results of consumer surveys that have shown that the ingestion or inhalation of cigarette filter fibres are a health concern to nearly all smokers”. As taken from Pauly JL et al. Tob Control. 2002, Mar; 11 Suppl 1:I51-61. PubMed, 2009 available at http://www.ncbi.nlm.nih.gov/pubmed/11893815

6. Functional effects on

6.1. Broncho/pulmonary system

Aerodynamic diameter measurement of cellulose acetate fibers from cigarette filters: what is the potential for human exposure? (Abstract). Aerodynamic diameter is a major determinant of particle and fiber deposition and toxicity in the respiratory tract. To characterize cellulose acetate fibers released from the filter end of cigarettes puffed under conditions approximating smoking, we designed multistage impactors to determine the aerodynamic diameters of large fibers with circumscribed diameters between 20 and 35 microm and aspect ratios ranging from subfiber ratios up to 40. This range of diameters encompasses all of the cellulose acetate fiber sizes that are commercially manufactured. When commercially available cigarettes with filters made from acetate fibers in this circumscribed diameter range were puffed directly into the impactor, on average 10 fibers/cigarette were released and their aerodynamic diameters were determined. In our studies, we found that the aerodynamic diameters of the cellulose acetate fibers were always greater than 23 microm. Using standard lung deposition models, we concluded that the fibers are nonrespirable with a very low probability of penetration to the distal lung. Our findings, which demonstrate release of only a small number of these large fibers with an extremely low likelihood of reaching the distal lung, indicate that these fibers are not a risk for human lung disease." As taken from Collazo H et al. Inhal Toxicol. 2002 Mar;14(3):247-62. PubMed, 2009 available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12028815&query_hl=19&itool=pubmed_docsum

Assessment of the elution of charcoal, cellulose acetate, and other particles from cigarettes with charcoal and activated charcoal/resin filters (Abstract). This experiment was designed to study the release of cellulose acetate fibers, charcoal, and other particles from cigarettes with charcoal and activated charcoal/resin filters. For the first time in such studies, efforts were made to identify the particles that were eluted using other analytical techniques in addition to light microscopy. Other corrective measures were also implemented. During the studies it was found that trimming of larger filters to fit smaller filter housings introduced cellulose acetate**-**like particles from the fibers of the filter material. Special, custom made-to-fit filters were used instead. Tools such as forceps that were used to retrieve filters from their housings were also found to introduce fragments onto the filters. It is believed that introduction of such debris may have accounted for the very large number of cellulose acetate and charcoal particles that had been reported in the literature. Use of computerized particle-counting microscopes appeared to result in excessive number of particles. This could be because the filter or smoke pads used for such work do not have the flat and level surfaces ideal for computerized particle-counting microscopes. At the high magnifications that the pads were viewed for particles, constant focusing of the microscope would be essential. It was also found that determination of total particles by using extrapolation of particle count by grid population usually gave extremely high particle counts compared to the actual number of particles present. This could be because particle distributions during smoking are not uniform. Lastly, a less complex estimation of the thickness of the particles was adopted. This and the use of a simple mathematical

conversion coupled with the Cox equation were utilized to assess the aerodynamic diameters of the particles. Our findings showed that compared to numbers quoted in the literature, only a small amount of charcoal, cellulose acetate shards, and other particles are released. It was also shown that those particles would have a low likelihood of reaching the lung.
As taken from Agyei-Aye K et al. Inhal Toxicol. 2004, Aug; 16(9):615-35. PubMed, 2009 available at http://www.ncbi.nlm.nih.gov/pubmed/16036754

6.2. Cardiovascular system

"Cellulose acetate has been found to possess the ability to activate platelets of patients hemodialysed with dialyzer containing a cellulose acetate membrane, as well as other cellulosic membranes." As taken from Cases A et al. Artif Organs. 1997 Apr;21(4):330-4. PubMed, 2009 available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9096808&query_hl=15&itool=pubmed_docsum

"Gene expression of transforming growth factor-beta (TGF-beta) is needed to induce expression of transcription factor forkhead box P3 (Foxp3), which is required for the development and function of regulatory T (Treg) cells. The number of circulating Treg cells and the level of Foxp3 expression increase during granulocyte and monocyte apheresis (GMA), a useful therapy for ulcerative colitis. However, the mechanism underlying GMA-induced Foxp3 expression is unknown. We found that the level of TGF-beta mRNA in peripheral blood mononuclear cells (PBMCs) was augmented just after treatment of peripheral blood with a GMA carrier, cellulose acetate beads, in vitro and that Foxp3 expression in PBMCs increased after culturing these cells for 5 days after the treatment. The augmentation of TGF-beta expression was observed in CD3(-) PBMCs but not in CD3(+) T cells. Furthermore, the increase in Foxp3 expression in T cells depended on co-culture with CD3(-) PBMCs. We conclude that cellulose acetate beads have an ability to induce Foxp3 expression in peripheral blood T cells via augmentation of TGF-beta expression in CD3(-) PBMCs". As taken from Jimma F et al. 2010. J. Clin. Apher. 25, 216-222. PubMed, 2013 available at http://www.ncbi.nlm.nih.gov/pubmed/20544711?dopt=AbstractPlus

6.3. Nervous system

No data available to us at this time.

6.4. Other organ systems, dependent on the properties of the substance

“REACTION OF VAGINAL TISSUE OF RABBITS TO INSERTED SPONGES MADE OF ACETYLCELLULOSE. VAGINAL WALL & ITS MUCOSAL LINING SHOWED SIGNS OF CYTOTOXICITY, EXTRACTS OF SPONGES TESTED FOR CYTOTOXICITY SHOWED SIGNIFICANT INHIBITION OF (3)H-THYMIDINE UPTAKE.”

As taken from HSDB, 2002

“We studied the action of rinse solutions from cellulose acetate hemodialyzers on isolated mitochondria. We showed that concentrates from the rinses impaired the adenosine 5'-triphosphate (ATP) synthesis as reflected by the decrease in respiration during state 3 and in P/O ratio. This impairment results from a calcium release from mitochondria that is induced by rinse solution concentrates. The release, triggering the mitochondrial calcium carrier, would explain the decrease in ATP synthesis. Moreover, rinse solution concentrates hinder mitochondrial calcium storage. The rise in cytosolic calcium in hemodialyzed patients may be related, at least in part, to these findings, since a lack of ATP impairs the ATP-dependent cellular calcium-extrusion pumps. We also showed that calcium channel blockers, at therapeutically relevant doses, restore ATP synthesis and calcium storage in mitochondria impaired by rinse solution concentrates. Finally, these in vitro results were confirmed by experiments on cells in culture proving that Diltiazem counteracts the cytotoxicity of rinse solution concentrates. These findings are consistent with observations that these drugs suppress the increase in leukocyte cytosolic calcium in dialyzed patients. Moreover, this would help explain the efficiency of calcium channel blockers in cells without L-calcium channels.” As taken from Tabouy LJ et al. Kidney Int. 1997 Nov; 52(5):1381-9. PubMed, 2009 available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9350663&query_hl=17&itool=pubmed_docsum

“Following adverse clinical events involving seven patients undergoing renal dialysis using 12-year-old cellulose acetate hemodialyzers, this in vitro study was proposed in an effort to characterize the inflammatory response to the constituent cellulose acetate (CA) fiber materials. Chemiluminescence (CL) and apoptosis assays were used to determine whether human neutrophils were activated by CA fiber materials and/or are sensitive to degradation/alteration of these fibers over time. Furthermore, the study examined in vitro assays with human neutrophils using a CA film, the solvents used in the film preparation and CA resin. The film could be cut to identical sized pieces in an effort to compare hemodialysis material effects in standardized amounts. For the CL assays, 60-min exposure was followed by secondary stimulation with n-formyl-met-leu-phe (fMLP) or phorbol-12-myristate-13-acetate (PMA). Short-term exposure (60-min postintroduction to CA materials) increased the inflammatory response as measured by the respiratory burst of neutrophils ($p < or =.05$), with CA fiber exposure significantly compared with cells alone. There was a trend toward an increased response with exposure to older fibers with secondary PMA stimulation. Apoptosis was increased 12% with exposure to the more aged fibers versus 2% with the new fibers. The fiber storage component, glycerol, significantly inhibited the oxidative response ($p < or =.001$; > or =80% suppression with concentrations of 5-20%). The solvents used in film preparation, N,N-dimethylacetamide and tetrahydrofuran, produced greater than a 70% and 60% suppression, respectively, of CL activity for all

concentrations > or =1%. More work is needed to determine the specific nature of the interaction of inflammatory cells with CA materials, but early evidence suggests that neutrophils are activated by CA and display an altered response to more aged fibers." As taken from Moore MA et al. J Biomed Mater Res. 2001 Jun 5; 55(3):257-65. PubMed, 2009 available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11255178&query_hl=21&itool=pubmed_docsum

"Dramatic improvements in clinical symptoms of rheumatoid arthritis and ulcerative colitis were observed after patients received granulocyte and monocyte adsorptive apheresis with a column containing cellulose acetate (CA) beads as adsorptive carriers. This study was to investigate the effect of CA beads on the generation of anti-inflammatory and pro-inflammatory cytokines in human blood. We incubated human whole blood with CA beads at 37 degrees C for up to 2 h and measured tumour necrosis factor-alpha (TNF-alpha) interleukin-1beta (IL-1beta) and IL-1 receptor antagonist (IL-1ra) produced by leucocytes. IL-1ra was also measured at the inflow and outflow of a column containing CA beads as leucocyte adsorptive carriers for the treatment of patients with ulcerative colitis. CA beads induced significant release of IL-1ra from leucocytes, but not TNF-alpha or IL-1beta. In contrast, all three cytokines were released when leucocytes were stimulated with lipopolysaccharide. IL-1ra was also markedly elevated in the outflow of the leucocyte apheresis column. These results indicate that CA beads selectively induce IL-1ra release from leucocytes which should contribute to the anti-inflammatory effect of granulocyte and monocyte adsorptive apheresis with CA beads as apheresis carriers." As taken from Takeda Y et al. Inflamm Res. 2003 Jun; 52(7):287-90. PubMed, 2009 available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12861393&query_hl=25&itool=pubmed_docsum

7. Addiction

JTI is not aware of any information that demonstrates that this ingredient has any addictive effect.

8. Burnt ingredient toxicity

No data available to us at this time.

9. Heated/vapor emissions toxicity

No data available to us at this time.

10. Ecotoxicity

10.1. Environmental fate

Biodegradation:

The influence of degree of substitution on blend miscibility and biodegradation of cellulose acetate blends (Abstract). In this account, we report our findings on blends of cellulose acetate having a degree of substitution (DS) of 2.49 (CA2.5) with a cellulose acetate having a DS of 2.06 (CA2.0). This blend system was examined over the composition range of 0-100% CA2.0 employing both solvent casting of films (no plasticizer) and thermal processing (melt-compressed films and injection molding) using poly(ethylene glycol) as a common plasticizer. All thermally processed blends were optically clear and showed no loss in optical quality after storage for several months. Thermal analysis and measurement of physical properties indicate that blends in the middle composition range are partially miscible, while those at the ends of the composition range are miscible. We suggest that the miscibility of these cellulose acetate blends is influenced primarily by the monomer composition of the copolymers. As taken from BUCHANAN CM et al. JOURNAL OF ENVIRONMENTAL POLYMER DEGRADATION; 4 (3). 1996. 179-195 available at http://www.springerlink.com/content/m057j3h070g03242/

The Ecological Categorization Results from the Canadian Domestic Substances List simply state that cellulose acetate is of uncertain persistence in the environment.

Data accessed March 2017 on the OECD website: http://webnet.oecd.org/CCRWeb/Search.aspx

10.2. Aquatic toxicity

The Ecological Categorization Results from the Canadian Domestic Substances List simply state that cellulose acetate is not inherently toxic to aquatic organisms and is of low ecotoxicological concern.

Data accessed March 2017 on the OECD website: http://webnet.oecd.org/CCRWeb/Search.aspx.

10.3. Sediment toxicity

Biodegradation of cellulose acetate by Neisseria sicca (Abstract) Bacteria capable of assimilating cellulose acetate**,** strains SB and SC, were isolated from soil on a medium containing cellulose acetate as a carbon source, and identified as Neisseria sicca. Both strains degraded cellulose acetate membrane filters (degree of substitution, DS, mixture of 2.8 and 2.0) and textiles (DS, 2.34) in a medium containing cellulose acetate (DS, 2.34) or its oligomer, but were not able to degrade these materials in a medium containing cellobiose octaacetate. Biodegradation of cellulose acetate (DS, 1.81 and 2.34) on the basis of biochemical oxygen demand reached 51 and 40% in the culture of N. sicca SB and 60 and 45% in the culture of N. sicca SC within 20 days. A decrease in the acetyl content of degraded cellulose acetate films and powder was confirmed by infrared and nuclear magnetic resonance analyses. After 10-day cultivation of N. sicca SB and SC, the number-average molecular weight of residual cellulose acetate decreased by 9 and 5%, respectively. Activities of enzymes that released acetic acid and produced reducing sugars from cellulose acetate were mainly present in the culture supernatant. Reactivity of enzymes for cellulose acetate (DS, 1.81) was higher than that for cellulose acetate (DS, 2.34).
As taken from Sakai K et al. Biosci Biotechnol Biochem. 1996, Oct; 60(10):1617-22. PubMed, 2009 available at http://www.ncbi.nlm.nih.gov/pubmed/8987659

10.4. Terrestrial toxicity

“Birds are known to respond to nest-dwelling parasites by altering behaviours. Some bird species, for example, bring fresh plants to the nest, which contain volatile compounds that repel parasites. There is evidence that some birds living in cities incorporate cigarette butts into their nests, but the effect (if any) of this behaviour remains unclear. Butts from smoked cigarettes retain substantial amounts of nicotine and other compounds that may also act as arthropod repellents. We provide the first evidence that smoked cigarette butts may function as a parasite repellent in urban bird nests. The amount of cellulose acetate from butts in nests of two widely distributed urban birds was negatively associated with the number of nest-dwelling parasites. Moreover, when parasites were attracted to heat traps containing smoked or non-smoked cigarette butts, fewer parasites reached the former, presumably due to the presence of nicotine. Because urbanization changes the abundance and type of resources upon which birds depend, including nesting materials and plants involved in self-medication, our results are consistent with the view that urbanization imposes new challenges on birds that are dealt with using adaptations evolved elsewhere”. As taken from Suarez-Rodrigues M et al. 2012. Biol. Letts 9. PubMed 2013 available at http://www.ncbi.nlm.nih.gov/pubmed/23221874

10.5. All other relevant types of ecotoxicity

The Ecological Categorization Results from the Canadian Domestic Substances List simply state that cellulose acetate has uncertain bioaccumulative potential in the environment.

Data accessed March 2017 on the OECD website: http://webnet.oecd.org/CCRWeb/Search.aspx

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13. Last audited

June 2020

Substance	*ID Code*	*Rpt No.*	*Year*	*Conclusion**	*21 CFR Section*
Cellulose acetate	9004-35-7	25	1973	2	182.90

SCOGS Opinion:

Cellulose is a major constituent of many foods of plant origin. As such it is a significant portion of the diet, but is neither degraded nor absorbed. Cellulose derivatives considered in this report are virtually unabsorbed and little or no degradation of absorbed and little or no degradation of absorbable products occurs in the human digestive tract. In man, consumption of large amounts appears to have no effect other than providing dietary bulk, reducing the nutritive value of such foodstuffs and possibly exerting a laxative effect. However, the existence of certain data and the different categorization of cellulose and the several cellulose derivatives on the GRAS list suggest that the Select Committee should render a separate opinion on each substance considered in this report.

A. CELLULOSE, MICROCRYSTALLINE CELLULOSE

Although pure cellulose and regenerated cellulose, including microcrystalline cellulose are not on the GRAS list, there is nothing in the available information to suggest that such forms of cellulose have significantly different biological properties that distinguish these forms of cellulose from those currently considered as GRAS or from naturally occurring cellulose. In view of the foregoing, the Select Committee concludes that: There is no evidence in the available information on pure and regenerated cellulose, including microcrystalline cellulose, that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current, or that might reasonably be expected in future.

B. METHYL CELLULOSE

In humans, virtually 100 percent of orally ingested methyl cellulose can be recovered in the feces withihn four days, indicating that absorption does not occur. However, in pregnant mice, very high doses of methyl cellulose, while not teratogenic, cause a significant increase in maternal mortality and retardation of fetal maturation. Such increased maternal and fetal toxicity does not occur at a dose of methyl cellulose which is 26-fold (or more) greater than that estimated to be the average daily adult dietary intake. It is noteworthy in this regard that similar toxic effects have been observed in identical tests performed by the same investigators on a large number of other polysaccharides fed at very high doses. The relative sensitivity of the several animal species to these effects varies, depending on the particular polysaccharide tested, but in all cases very large doses are required. Until these effects have been adequately explained, it appears to be inappropriate to conclude that unrestricted use of such substances in food would be without hazard. In the light of the foregoing, the Select Committee concludes that: There is no evidence in the available information on methyl cellulose that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public

when it is used at levels that are now current and in the manner now practiced. However, it is not possible to determine, without additional data, whether a significant increase in consumption would constitute a dietary hazard.

C. CARBOXYMETHYL CELLULOSE

Carboxymethyl cellulose is converted spontaneously to a salt in alkaline solution, and it is probable that the distinction between carboxymethyl cellulose and its salts is artificial. However, carboxymethyl cellulose is liested as GRAS as a substance migrating to food from cotton or cotton fabrice used in dry foods packaging, while its sodium salt is listed as GRAS as a miscellaneous or general purpose food additive. In view of the separate listing of carboxymethyl cellulose, the Select Committee concludes that: There is no evidence in the available information on carboxymethyl cellulose that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when it is used in dry food packaing materials originating from cotton or cotton fabrics as now practed or as it might reasonably be expected to be used for such purposes in future.

D. SODIUM CARBOXYMETHYL CELLULOSE

Despite the probable lack of distinction between sodium carboxy methyl cellulose and its parent compound, carboxymethyl cellulose, only the sodium carboxymethyl cellulose is GRAS as a miscellaneous and general purpose food additive. As such, there are no data that suggest it reacts differently than pure and regenerated cellulose or carboxymethyl cellulose. In view of the foregoing the Select Committee concludes that: There is no evidence in the available information on sodium carboxymethyl cellulose that demonstrtes, or suggests reasonable grounds to suspect, a hazard to the public when it is used at levels that are now current or that might reasonably be expected in future.

E. HYDROXYPROPYLMETHYL CELLULOSE

Hydroxypropylmethyl cellulose is not listed as GRAS. It is a food additive used as a thickening agent, stabilizer and emulsifier. Hydroxypropylmethyl cellulose is sinthesized from methyl cellulose by the action of alkali and propylene oxide. There are no data available to suggest that hydroxypropylmethyl cellulose possesses adverse health effects; however, teratology studies dimilar to those conducted with mehtyl cellulose are not available for its hydroxypropyl derivative. Therefore, it is suggested that, in due course, appropriate studies should be conducted with hydroxypropylmethyl cellulose. The Select Committee has weighed the foregoing and concludes that: There is no evidence in the available information on hydroxypropylmethyl cellulose that demonstrates, or suggested reasonable grounds to suspect, a hazard to the public when it is used at levels that are now current and in the manner now practiced (21 CFR 121.1021)

F. ETHYL CELLULOSE AND CELLULOSE ACETATE

There is a paucity of data concerning possible adverse health effects of ethyl cellulose and cellulose acetate. both are

Substance	*ID Code*	*Rpt No.*	*Year*	*Conclusion**	*21 CFR Section*

included in the GRAS list as substances migrating to food from paper or paperboard products used in food packaging. According to the NRC survey (6), very small amounts of ethyl cellulose also appear to be used in hard candy and chewing gum. In the GRAS context, the quantity of ethyl cellulose or cellulose acetate migrating to foods from packaging would be orders of magnitude below the levels of cellulose and cellulose derivaties now known to occur in foods. In the light of the foregoing, the Select Committee concludes that: There is no evidence in the available information on ethyl cellulose and cellulose acetate that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used in food packaging materials as now practiced or as they might be expeccted to be used for such purposes in future.

**** denotes Type of Conclusion 1, 2, 3, 4, or 5. Definitions of conclusion types can be found at the end of this report..***

Final Report of the Cosmetic Ingredient Review Expert Panel

Amended Safety Assessment of Cellulose and Related Polymers as used in Cosmetics

March 23, 2009

The 2009 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D. This report was prepared by Valerie C. Robinson, Scientific Analyst and Writer.

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Amended Safety Assessment of Cellulose and Related Polymers as Used in Cosmetics

Abstract: An earlier safety assessment of several cellulose polymers has been expanded to include cellulose itself and other cellulose polymers used in cosmetics. In general, these ingredients are modified cellulose polymers formed by reaction with the free hydroxyl groups in cellulose. The number of hydroxyl groups reacting, as well as the nature of the substitute group, largely determine the physical properties, particularly solubility, of the product. These ingredients are used in a wide variety of cosmetics as thickeners, suspending agents, film formers, stabilizers, emulsifiers, emollients, binders, or water-retention agents. These ingredients do not appreciably penetrate the skin barrier. Cellulose and its polymers pass essentially unchanged through the gastrointestinal tract following oral administration and are practically non-toxic. Ocular and dermal irritation studies indicate, at most, minimal irritants and not sensitizers. These ingredients are considered safe as cosmetic ingredients in the practices of use and concentration given in this safety assessment.

INTRODUCTION

The Cosmetic Ingredient Review (CIR) Expert Panel evaluated the safety of Hydroxyethylcellulose, Hydroxypropylcellulose, Methylcellulose, Hydroxypropyl Methylcellulose, and Cellulose Gum as used in cosmetics, concluding that these ingredients are "safe as cosmetic ingredients in the present practices of use and concentration" (Elder 1986).

The CIR Expert Panel has further considered other related ingredients and determined that the available data support the safety of cellulose and a larger group of modified cellulose polymers. Accordingly, the CIR Expert Panel is amending the original safety assessment (Elder 1986) to include other ingredients.

Therefore, this report addresses the safety of:

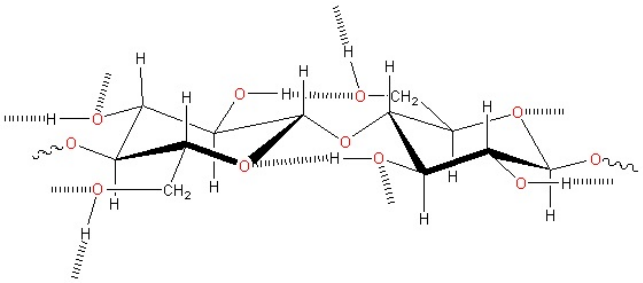
- Calcium Carboxymethyl Cellulose,
- Carboxymethyl Cellulose Acetate Butyrate,
- Carboxymethyl Hydroxyethylcellulose,
- Cellulose,
- Cellulose Acetate,
- Cellulose Acetate Butyrate,
- Cellulose Gum,
- Cellulose Acetate Propionate,
- Cellulose Acetate Propionate Carboxylate,
- Cellulose Succinate,
- Cetyl Hydroxyethylcellulose,
- Ethylcellulose,
- Hydrolyzed Cellulose Gum,
- Hydroxybutyl Methylcellulose,
- Hydroxyethylcellulose,
- Hydroxyethyl Ethylcellulose,
- Hydroxypropylcellulose,
- Hydroxypropyl Methylcellulose,
- Hydroxypropyl Methylcellulose Acetate/Succinate,
- Methylcellulose,
- Methyl Ethylcellulose,
- Methyl Hydroxyethylcellulose,
- Microcrystalline Cellulose,
- Potassium Cellulose Succinate, and
- Sodium Cellulose Sulfate.

CHEMISTRY

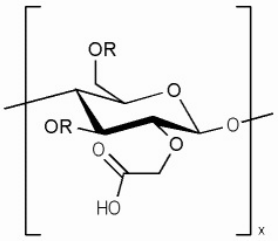
Definition and Structure

The structure of cellulose is shown in **Figure 1a**. By comparison, the structure for Carboxymethyl Cellulose Acetate Butyrate as given in the *International Cosmetic Ingredient Dictionary and Handbook* (Gottachalck and Bailey 2008), where R represents hydrogen or the acetyl or butyryl moiety, is shown in **Figure 1b**.

According to Hake and Rowe (1963), Hydroxyethylcellulose, Hydroxypropylcellulose, Methylcellulose, Hydroxypropyl Methylcellulose, and Cellulose Gum are modified cellulose polymers. 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 are odorless, tasteless, and chemically stable.



(a)



(b)

Figure 1. a) structure for Cellulose; b) structure for Carboxymethyl Cellulose Acetate Butyrate, where R represents hydrogen or the acetyl or butyryl moiety.

As given in the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and Bailey 2008), ingredients included in this safety assessment are ethers, as for Cellulose Gum; salts of ethers, as for Calcium Carboxymethyl Cellulose; esters, as for Cellulose Acetate; modified cellulose polymers, as for Hydroxyethylcellulose; or the salts of sulfated cellulose, as for Sodium Cellulose Sulfate. In one case, Microcrystalline Cellulose, the definition describes a physical form of cellulose.

These definitions are listed in **Table 1**.

Physical and Chemical Properties

Table 2 lists physical and chemical properties for Cellulose Gum, Hydroxypropylcellulose, Hydroxypropyl Methylcellulose, and Methylcellulose.

Table 1. Definitions of Cellulose and modified cellulose polymers as given in the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and Bailey 2008).

Ingredient	CAS No.	Definition
Calcium Carboxymethyl Cellulose	9050-04-8	calcium salt of the carboxymethyl ether of Cellulose (q.v.).
Carboxymethyl Cellulose Acetate Butyrate	none listed	product obtained by the reaction of butyric and acetic anhydrides with carboxymethyl cellulose.
Carboxymethyl Hydroxyethylcellulose	9004-30-2	ethylene glycol ether of Cellulose Gum (q.v.).
Cellulose	9004-34-6	natural polysaccharide derived from plant fibers.
Cellulose Acetate	9004-35-7	acetic acid ester of Cellulose (q.v.).
Cellulose Acetate Butyrate	9004-36-8	butyric acid ester of a partially acetylated cellulose.
Cellulose Gum	9004-32-4	sodium salt of the polycarboxymethyl ether of Cellulose (q.v.).
Cellulose Acetate Propionate	9004-39-1	propionic acid ester of a partially acetylated cellulose.
Cellulose Acetate Propionate Carboxylate	none listed	product obtained by ozone oxidation of Cellulose Acetate Propionate (q.v.).
Cellulose Succinate	none listed	ester of Cellulose (q.v.) and Succinic Acid (q.v.).
Cetyl Hydroxyethylcellulose	none listed	ether of Cetyl Alcohol (q.v.) and Hydroxyethylcellulose (q.v.).
Ethylcellulose	9004-57-3	ethyl ether of cellulose.
Hydrolyzed Cellulose Gum	none listed	hydrolysate of Cellulose Gum (q.v.) obtained by acid, enzyme or other method of hydrolysis.
Hydroxybutyl Methylcellulose	9041-56-9	butylene glycol ether of Methylcellulose (q.v.).
Hydroxyethylcellulose	9004-62-0	modified cellulose polymer which contains hydroxyethyl side chains.
Hydroxyethyl Ethylcellulose	9004-58-4	ethylene glycol ether of Ethyl Cellulose (q.v.).
Hydroxypropylcellulose	9004-64-2	propylene glycol ether of cellulose.
Hydroxypropyl Methylcellulose	9004-65-3	propylene glycol ether of Methylcellulose (q.v.).
Hydroxypropylmethylcellulose Acetate/Succinate	71138-97-1	reaction product of succinic anhydride and acetic anhydride with Hydroxypropyl Methylcellulose (q.v.).
Methylcellulose	9004-67-5	methyl ether of cellulose.
Methyl Ethylcellulose	9004-59-5	methyl ether of Ethylcellulose (q.v.).
Methyl Hydroxyethylcellulose	9032-42-2	methyl ether of Hydroxyethylcellulose (q.v.).
Microcrystalline Cellulose	9004-34-6	isolated, colloidal crystalline portion of cellulose fibers.
Potassium Cellulose Succinate	none listed	potassium salt of Cellulose Succinate (q.v.).
Sodium Cellulose Sulfate	9005-22-5	sodium salt of sulfated Cellulose (q.v.).

Cellulose interactions with water have been considered to play an important role in chemistry, physics, and technology of Cellulose isolation and processing, such as papermaking (Watanabe et al. 2006). Suppasrivasuseth et al. (2006) reported that Cellulose membranes are thin and highly permeable to water.

Cellulose Gum is the sodium salt of carboxymethylcellulose. Because carboxymethylcellulose is spontaneously converted to the sodium salt in alkaline solution, much of the literature makes no distinction between the two (Federation of American Societies for Experimental Biology 1974).

According to CTFA (1982), Cellulose Gum is stable under typical cosmetic use conditions. Klose and Glicksman (1972) reported that this ingredient exhibits a reversible loss of viscosity on heating. Solutions are fairly stable between pH 5 and 11.

Cellulose Gum is compatible with most other water-soluble gums and is generally unaffected by high concentrations of monovalent salts. It forms clear films that are resistant to oils and most organic soIvents.

Ethylcellulose compactibility becomes a key factor in controlled-release dosage forms, in the absence of polymer swelling ability, because kinetics would depend largely on the porosity of the hydrophobic compact (Emeje et al. 2006). Ethylcellulose is considered insoluble in water, but it can take up water. This is because of its hydrogen bonding capability with water due to the polarity difference between the oxygen atom and the ethyl group of the polymer.

Table 2. Chemical and physical properties of Cellulose Gum, Hydroxypropylcellulose, Hydroxypropyl Methylcellulose, and Methylcellulose (Elder 1986)

Property	Values for:				
	Cellulose Gum	**Hydroxyethylcellulose**	**Hydroxypropylcellulose**	**Hydroxypropyl Methylcellulose**	**Methylcellulose**
Appearance	white to cream colored, odorless, tasteless powder	white, ororless, tasteless powder	white, odorless, tasteless granular powder	white to off-white fibrous powder	white to off-white, odorless, tasteless, fibrous powder
Weight per anhydroglucose unit (Da)	185 - 258	206 (minimum)	223 (minimum)	177 - 279	166.3 - 190.5
pH					
1% aq. soltn.	6.5 - 8.5	6.5 - 8.5	6.5 - 8.5	- [a]	-
2% aq. soltn.	7.5	6.0 - 8.0	5.0 - 8.5	-	-
5% aq. soltn.	-	6.0 - 8.5	-	-	-
Viscosity (cps) [b]					
1% solids	69 - 5000	800 - 5000	40 - 2500	8	-
2% solids	10 - 50000	25 - 6500	75 - 6500	10 - 8000	10 - 8000
5% solids	115000	75 - 400	25 - 400	400	-
10% solids	-	-	100 - 700	-	-
Particle size (mesh sizing)				-	-
through 40	-	90% (minimum)	-	-	-
through 30	-	-	95% (minimum)	-	-
through 20	-	-	99% (minimum)	-	-
Density (g/ml)	0.75	-	0.5	0.25 - 0.7	0.25 - 0.7
Moisture (max.)	8 - 10 %	5%	5%	3 - 5%	3 - 5%
Ash (max.)	-	5%	0.5%	1.5 - 3%	1.5 - 2%
Heavy metals (max.. total)	40 ppm	-	40 ppm	10 ppm	10 ppm
Lead	10 ppm	-	10 ppm	10 ppm	10 ppm
Arsenic	3 ppm	-	3 ppm	3 ppm	3 ppm
Refractive index [c]	-	1.337	1.336	1.336	-
Specific gravity					
1% aq.	-	-	-	1.0112	1.0112
5% aq.	-	-	-	1.0117	1.0117
10% aq.	-	-	-	1.0245	1.0245
Solubility					
water	soluble; disperses	soluble	soluble up to 40° C; insoluble > 40° C	soluble in the cold only	soluble in the cold only
alcohol	insoluble	soluble up to 70° C	soluble	-	insoluble [e]
organic	insoluble	soluble [d]	soluble in polar solvents	soluble in polar solvents	soluble [e]
Surface tension in water (dynes/cm)	71	64	45	50	-
Film properties					
tensile strength	12000 psi	4000 psi	2000 psi	3000 psi	-
elongation at break	10%	25%	50%	35%	-
flexibility [f]	poor	good	excellent	good	-
equilibrium moisture content [f]	15%	6%	3%	4%	-
blocking tendency [g]	considerable	some	none	little	-
film density	1.59 g/ml	-	-	-	-
Minimum ignition temperature	-	429° C	-	-	-

[a] a dash means the data were not available; [b] at 25° C; [c] 2% aqueous at 20°C; [d] in dimethylsulfoxide only; [e] in glacial acetic acid and in equal parts of ethanol and chloroform, but insoluble in chloroform alone; [f] at 50% relative humidity; [g] at 90% relative humidity.

Hydroxyethylcellulose is prepared by reacting alkali cellulose with ethylene oxide in the presence of alcohol or acetone. The molar substitution (MS), is the average number of moles of ethylene oxide attached to the anhydroglucose cellulose unit at either the hydroxyl groups in the chain or at previously reacted hydroxyl groups. The degree of substitution (DS) is the average number of hydroxyl groups substituted per anhydroglucose unit. Hydroxyethylcellulose is commonly manufactured with an MS of 1.8 and 2.5; 2.5 gives optimum water solubility and strong resistance to enzymic attack (Rufe 1975; Haugen et al. 1978). However, the various grades range from an MS of 1.5 to 3.0. Solution viscosities vary greatly within each MS level (Rufe 1975); the DS ranges from 1.5 to 3 (max = 3) (CTFA 1982). Other specific grades of Hydroxyethylcellulose may contain additives to delay hydration, prevent lumping, and retard bacterial growth. Hydroxyethylcellulose can be identified by close matching to a standard infrared spectrum with no indication of foreign materials (CTFA 1982).

Being nonionic in character, Hydroxyethylcellulose does not react with polyvalent cations, and in solution is generally unaffected by moderate shifts in pH. Hydroxyethylcellulose 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 (Rufe 1975; Kostolowska et al. 1981). Increased flocculating action on kaolin suspensions has been demonstrated by Hydroxyethylcellulose graft copolymerized with acrylamide (Miyata et al. 1975).

Haugen et al. (1978) studied the steady shear flow properties, rheological reproducibility, and stability of aqueous Hydroxyethylcellulose dispersions over a period of 5 years. Dispersions of 1.5-3.5% Hydroxyethylcellulose 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.

Hydroxyethylcellulose is stable under the typical conditions of cosmetic use (CTFA 1982), but is susceptible to bacterial degradation and must be properly preserved for long-term stabiIity (Klose and Glicksman 1972). Eros and Csordas (1979) studied the effect of various preservatives and temperatures on the viscosity and stability of Hydroxyethylcellulose solutions over a 3-month period. The solution preserved with methyl 4-hydroxybenzoate remained nearly unchanged, whereas those without preservatives had significant decreases in viscosity related to time. The viscosity of all solutions decreased exponentially with temperature increase.

Hydroxyethylcellulose has demonstrated synergistic viscosity when combined with an equal amount of an anionic cellulose derivative. The resultant viscosity has been almost double that expected. Hydroxyethylcellulose (viscosity of 1800 cps) combined with Cellulose Gum (viscosity of 1500 cps) had an actual viscosity of 3200 cps when the expected viscosity was 1650 cps (Rufe 1975).

Hydroxypropylcellulose can be identified by close matching to a standard infrared spectrum with no indication of foreign materials (Estrin et al. 1982).

Hydroxypropylcellulose is stable under typical cosmetic use conditions (CTFA 1982). Hydroxypropylcellulose 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 Hydroxypropylcellulose exhibit Newtonian behavior at low shear rates but become more thixotropic at high shear rates. Hydroxypropylcellulose is very surface-active, has good film-forming properties, and forms films with excellent flexibility and heat-sealing properties (Klose and Glicksman 1972). Hydroxypropylcellulose is particularly useful as an emulsifier and thickener in oil-in-water emulsions (Rufe 1975; Klose 1972).

Hydroxypropyl Methylcellulose is a mixed alkyl hydroxyalkyl cellulose ether containing methoxyl and hydroxypropyl groups Merchant et al. (2006). The hydration rate of Hydroxypropyl Methylcellulose depends on the nature of these substituents, including the degree of substitution. The hydration rate increases with an increase in hydroxypropyl content. The solubility of Hydroxypropyl Methylcellulose is pH independent; it is available in a wide range of molecular weights.

Hydroxypropyl Methylcellulose is stable under typical cosmetic use conditions (CTFA 1982) Aqueous solutions are surface-active, form films upon drying, and exhibit thermogelling properties.

Methylcellulose is stable under typical cosmetic use conditions (CTFA 1982). Solutions of Methylcellulose 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 electrolytes, as well as sucrose, glycerol, and sorbitol, depress the gel point. Methylcellulose 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 (Klose and Glicksman 1972). 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 Methylcellulose (Klose and Glicksman 1972; Windholz 1983).

The chemical class, function in cosmetics, sources, technical names, and synonyms from the *International Cosmetic Ingredient Dictionary and Handbook* are given in **Table 3**.

Table 3. Chemical classes, functions in cosmetics, sources, technical names and synonyms for ingredients in this safety assessment as given in the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and Bailey 2008).

Ingredient	Chemical classes	Function(s) in cosmetics	Source	Technical/synonyms
Calcium Carboxymethyl Cellulose	gums	emulsion stabilizer	plant	calcium cellulose glycolate
	hydrophilic colloids and derivatives (including salts)	film-former	synthetic	cellulose, carboxymethyl ether, calcium salt
	organic salts	viscosity-increasing agent (aqueous)		
Carboxymethyl Cellulose Acetate Butyrate	carbohydrates	emulsion stabilizer	plant	none
	esters	film-former	synthetic	
		viscosity-increasing agent (aqueous)		

Table 3 (continued). Chemical classes, functions in cosmetics, sources, technical names and synonyms for ingredients in this safety assessment as given in the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and Bailey 2008).

Ingredient	Chemical classes	Function(s) in cosmetics	Source	Technical/synonyms
Carboxymethyl Hydroxyethylcellulose	gums	binder	plant	cellulose, carboxymethyl-2-hydroxyethyl ether, sodium salt
	hydrophilic colloids and derivatives (including salts)	emulsion stabilizer	synthetic	sodium carboxymethyl hydroxyethylcellulose
		film-former		
		viscosity-increasing agent (aqueous)		
Cellulose	biological polymers and their derivatives	absorbent	plant	cellulose powder
	carbohydrates	bulking agent		wood pulp, bleached
		slip modifier		
Cellulose Acetate	biological polymers and their derivatives	film former	plant	acetic acid, cellulose ester
	esters		synthetic	acetyl cellulose powder
Cellulose Acetate Butyrate	biological polymers and their derivatives	film former	plant	acetobutyrate cellulose
	esters		synthetic	acetylpropionylcellulose
				cellulose, acetate butanoate
				cellulose butyrate acetate
Cellulose Acetate Propionate	biological polymers and their derivatives	film former	plant	cellulose, acetate propanoate
	carbohydrates		synthetic	
	esters			
Cellulose Acetate Propionate Carboxylate	biological polymers and their derivatives	binder	plant	none
	carbohydrates	film former	synthetic	
	esters	emulsion stabilizer		
		viscosity increasing agents - aqueous		
Cellulose Gum	gums	binders	plant	acetic acid, hydroxy-, cellulose ether
	hydrophilic colloids and derivatives	film formers		carboxymethyl cellulose
		emulsion stabilizers		carboxymethylcellulose (RIFM)
		viscosity increasing agent - aqueous		carmellose (INN)
				cellulose, carboxymethyl ether
				cellulose, ether with glycolic acid, sodium salt
				sodium carboxymethyl cellulose
				sodium carmellose
				sodium CMC
Cellulose Succinate	carbohydrates	opacifying agents	plant	none
	esters	skin-conditioning agents - humectant		
Cetyl Hydroxyethylcellulose	gums	emulsion stabilizers	animal	cellulose, hexadecyl 2-hydroxyethyl ether
	hydrophilic colloids and derivatives	viscosity increasing agent - aqueous	plant	hexadecyl hydroxyethyl cellulose
			synthetic	
Ethylcellulose	carbohydrates	binder	plant	cellulose, ethyl ether
	ethers	film former		ethycellulose (INN)
		fragrance ingredient		ethylcellulose (RIFM)
		viscosity increasing agent - nonaqueous		
Hydrolyzed Cellulose Gum	gums	emulsion stabilizer	plant	none
	hydrophilic colloids and derivatives	film former	synthetic	
		viscosity increasing agent - aqueous		
Hydroxybutyl Methylcellulose	gums	binder	plant	cellulose, hydroxybutyl methyl ether
	hydrophilic colloids and derivatives	emulsion stabilizers	synthetic	
		film former		
		viscosity increasing agent - aqueous		

Table 3 (continued). Chemical classes, functions in cosmetics, sources, technical names and synonyms for ingredients in this safety assessment as given in the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and Bailey 2008).

Ingredient	Chemical classes	Function(s) in cosmetics	Source	Technical/synonyms
Hydroxyethylcellulose	gums	binder	plant	cellulose hydroxyethylate
	hydrophilic colloids and derivatives	emulsion stabilizers	synthetic	cellulose, 2-hydroxyethyl Ether
		film former		H.E. cellulose
		viscosity increasing agent - aqueous		
Hydroxyethyl Ethylcellulose	gums	adhesive	plant	cellulose ethyl hydroxyethyl ether
	hydrophilic colloids and derivatives	binder	synthetic	ethyl hydroxyethyl cellulose
		emulsion stabilizers		hydroxyethylcellulose ethylether
		film former		
		viscosity increasing agent - aqueous		
Hydroxypropylcellulose	gums	binder	plant	cellulose, 2-hydroxypropyl ether
	hydrophilic colloids and derivatives	emulsion stabilizers	synthetic	
		film former		
		viscosity increasing agent - aqueous		
		viscosity increasing agent - nonaqueous		
Hydroxypropyl Methylcellulose	gums	adhesive	plant	carbohydrate gum
	hydrophilic colloids and derivatives	binder	synthetic	cellulose, 2-hydroxypropyl methyl ether
		emulsion stabilizers		methyl hydroxypropyl cellulose
		film former		
		viscosity increasing agent - aqueous		
Hydroxypropyl Methylcellulose Acetate/Succinate	esters	film former	plant	cellulose, 2-hydroxypropyl methyl ether
	gums		synthetic	acetate hydrogen butanedioate
	hydrophilic colloids and derivatives			
Methylcellulose	gums	binder	plant	none
	hydrophilic colloids and derivatives	emulsions stabilizer	synthetic	
		film former		
		viscosity increasing agent - aqueous		
		viscosity increasing agent - nonaqueous		
Methyl Ethylcellulose	carbohydrates	binder	plant	cellulose, ethyl methyl ether
	ethers	film former	synthetic	ethyl methyl cellulose
		viscosity increasing agent - aqueous		
Methyl Hydroxyethylcellulose	gums	adhesive	plant	cellulose, 2-hydroxyethyl methyl ether
	hydrophilic colloids and derivatives	emulsions stabilizer	synthetic	
		viscosity increasing agent - aqueous		
Microcrystalline Cellulose	biological polymers and their derivatives	abrasive	plant	none
	carbohydrates	absorbent	synthetic	
		anti-caking agent		
		bulking agent		
		emulsions stabilizer		
		slip modifier		
		viscosity increasing agent - aqueous		
Potassium Cellulose Succinate	carbohydrates	opacifying agent	plant	none
	organic salts	skin-condtioning agent - humectant	synthetic	
Sodium Cellulose Sulfate	gums	binder	plant	cellulose sulfate salt
	hydrophilic colloids and derivatives	emulsions stabilizer	synthetic	
	sulfuric acid esters	viscosity increasing agent - aqueous		

Watanabe et al. (2006) investigated water absorption onto Microcrystalline Cellulose (MCC) in the moisture content range of 0.2 - 13.4 wt % by near-infrared spectroscopy. In order to distinguish heavily overlapping O-H stretching bands in the NIR region due to MCC and water, principal component analysis and generalized 2-dimensional correlation spectroscopy (2DCOS) were applied to the obtained spectra. The NIR spectra in 4 adsorption stages separated by PCA were analyzed by 2DCOS. For the low moisture content range of 0.2 - 3.1 wt %, a decrease in the free or weakly hydrogen-bonded MCC OH band, increases in the bonded MCC OH bands, and increases in the adsorbed water OH bands are observed. According to the authors, these results suggest that the inter- and intrachain H-bonds of MCC are formed by monomeric water molecule adsorption. In the moisture content range of 3.8 - 7.1 wt %, spectral changes in the NIR spectra reveal that the aggregation of water molecules starts at the surface of MCC. For the high moisture content range of 8.1 - 13.4 wt %, the NIR results suggested that the formation of bulk water occurred. It was also revealed that approximately 3 - 7 wt % of adsorbed water was responsible for the stabilization of the H-bond network in MCC at the cellulose-water surface.

Water-Based Emulsions

According to Sprockel et al. (1990), the water vapor transmission rates (WVTR) through solvent cast polymer films prepared from Cellulose Acetate, Cellulose Acetate Propionate, and Cellulose Acetate Butyrate were influenced by the relative humidity, substituent type and extent of substitution. Increasing the relative humidity from 32 to 90% increased the WVTR 3 to 5 times depending on the polymer used. The WVTR increased in the order of butyrate < propionate < acetate. An increase in the extent of substitution with acetyl and/or butyryl groups resulted in an exponential decline in the WVTR.

Akiyama et al. (2006) described the mechanism of oil-in-water emulsification using a water-soluble amphiphilic polymer HHM-HEC (hydrophobically-hydrophilically modified Hydroxyethylcellulose) and lipophilic surfactant. HHM-HEC was used as a thickener and a polymeric surfactant, and the addition of small quantities of various types of nonionic lipophilic surfactant (hydrophilic-lipophilic balance <5) decreased the droplet size of several types of oil due to a lowering of the tension at the water/oil interface. The oil droplets were held by the strong network structure of the aqueous HHM-HEC solution, preserving the O/W (oil-in-water) phase without inversion. These stable O/W emulsions were prepared without the addition of hydrophilic surfactants and therefore exhibited improved water repellency.

Method of Manufacture

According to Watanabe et al. (2006), Cellulose as used in cosmetics comes mainly from the cell walls of higher plants. The *International Cosmetic Ingredient Dictionary and Handbook* (Gotschalck and Bailey 2008), however, indicates a synthetic source for many of these ingredients.

Hydroxypropylcellulose is prepared commercially by reacting cellulose with sodium hydroxide and propylene oxide under proprietary conditions. The DS is usually 3 (CTFA 1982); the MS is usually greater than 3 (Klose and Glicksman 1973). Silicon dioxide (0.3%) may be added as an anticaking agent (CTFA 1982).

Cellulose Gum is manufactured by treating cellulose (cotton Iinters or wood pulp) with alkali followed by reaction with sodium monochloroacetate. The resulting product is then purified (CTFA 1982).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 (Klose and Glicksman 1972).

Methylcellulose 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 alkylation 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 (CTFA 1982). This is within the DS range that has maximum water solubility (Klose and Clicksman 1972).

Hydroxypropyl Methylcellulose 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 (CTFA 1982), with the number of methoxyl substitutions typically much larger than the number of hydroxypropyl substitutions (Rufe 1975).

Analytical Methods

According to Estrin et al. (1982), many of these ingredients may be identified by their infrared spectrum. Cellulose and modified cellulose polymers can be identified by close matching to a standard infrared spectrum with no indication of foreign materials. Cellulose Gum can be identified by close matching to the CTFA standard infrared spectrum with no indication of foreign material. Hydroxypropyl Methylcellulose can be identified by close matching to a standard infrared spectrum no indication of foreign materials. Methylcellulose can be identified by close matching to a standard infrared spectrum with no indication of foreign materials.

Impurities

Watanabe et al. (2006) suggested that 3 types of water (free water, freezing bound water, and nonfreezing bound water) are present in powdery celluloses prepared from natural Cellulose, such as cotton, wood, and linen Cellulose, on the basis of differential scanning calorimetry studies.

Nanoparticles

Perugini et al. (2002) studied the effect of nanoparticle encapsulation on the photostability of the sunscreen agent, *trans* 2-ethylhexyl-*p*-methoxycinnamate (*trans*- EHMC). Ethylcellulose and poly-D,L.-lactide-co-glycolide (PLGA) were used as biocompatible polymers for the preparation of the particulate systems. The “salting out” method was used for nanoparticle preparation and several variables were evaluated in order to optimize product characteristics. The photodegradation of the sunscreen agent in emulsion vehicles was reduced by encapsulation into the PLGA nanoparticles (the extent of degradation was 35.3% for the sunscreen-loaded nanoparticle compared to 52.3% for free *trans*-EHMC), whereas the Ethylcellulose nanoparticle system had no significant effect. The authors concluded that PLGA nanoparticles loaded with *trans*-EHMC improve the photostability of the sunscreen agent.

Ubrich et al. (2004) performed a comparative study which involved the preparation and characterization of propanolol hydrochloride nanoparticles. The water-in-oil-in-water (w/o/w) emulsification process is the method of choice for the encapsulation inside polymeric particles of hydrophilic drugs such as proteins and peptides which are high molecular weight macromolecules. The objective was to apply this technique in order to formulate nanoparticles loaded with both a hydrophilic and a low molecular weight drug, such as propanolol-HCl. Nanoparticles were prepared using a pressure homogenization device with various polymers (poly-ε-caprolactone, poly (lactide-co-glycolide), ethylcellulose. Different amounts of drug were compared to various polymers in terms of particle size, encapsulation efficiency and drug release.

Higher encapsulation efficiencies were obtained with both poly (ε-caprolactone) (PCL) (77.3%) and poly (D,L-lactic-co-glycolic

acid) PLGA (83.3%) compared to Ethylcellulose (66.8%). The in vitro drug release was characterized by an initial burst and an incomplete dissolution of the drug. When decreasing the polymer/drug ratio, the release appeared more controlled and prolonged up to 8 hours. The authors concluded that nanoparticles prepared by w/o/w emulsification followed by solvent evaporation might be potential drug carriers for low molecular weight and hydrophilic drugs (Ubrich et al. 2004).

Souto et al. (2004) evaluated the physical stability of solid lipid nanoparticles and nanostructured lipid carriers before and after incorporation into hydrogel formulations. In the study, aqueous dispersions of lipid nanoparticles were investigated as drug delivery systems for various therapeutic purposes. According to the authors, one of their interesting features is the possibility of topical use, for which these systems have to be incorporated into commonly used dermal carriers, such as creams or hydrogels, in order to have a proper semisolid consistency. Four different gel-forming agents (xanthan gum, Hydroxyethylcellulose 4000, Carbopol®943 and chitosan) were selected for hydrogel preparation. Aqueous dispersions of lipid nanoparticles - solid lipid nanoparticles and nanostructured lipid carriers - made from tripalmitan were prepared by hot high pressure homogenization and then incorporated into the freshly prepared hydrogels. Nanostructured lipid carriers differ from solid lipid nanoparticles due to the presence of a liquid lipid (Miglyol®812) in the lipid matrix. Lipid nanoparticles were physically characterized before and after their incorporation into hydrogels. The authors noted that it could be demonstrated that physical properties of the dispersed lipid phase have a great impact on the rheological properties of the prepared semisolid formulations. By employing an oscillation frequency sweep test, significant differences in elastic response of solid lipid nanoparticles and nanostructured lipid carrier aqueous dispersions were observed.

USE

Cosmetic

Currently, use of individual cosmetic ingredients as a function of product types is reported to the Food and Drug Administration (FDA) under the Voluntary Cosmetic Registration Program (VCRP) for each ingredient as a function of product type. The Cosmetic, Toiletry, and Fragrance Association (CTFA) and its successor organization, the Personal Care Products Council (Council) conducted surveys of cosmetics industry formulators to determine current use concentrations. **Table 4** provides the information available from the VCRP and from the industry survey.

No uses or use concentrations were available for:

- Calcium Carboxymethyl Cellulose,
- Cellulose Acetate Propionate,
- Cellulose Acetate Propionate Carboxylate,
- Cellulose Succinate,
- Hydrolyzed Cellulose Gum,
- Hydroxybutyl Methylcellulose,
- Hydroxypropylmethylcellulose Acetate/Succinate,
- Methyl Ethylcellulose,
- Potassium Cellulose Succinate, or
- Sodium Cellulose Sulfate.

An ingredient called Carboxymethyl Cellulose was reported under the VCRP to have 8 uses. This ingredient is not, however, given as a cosmetic ingredient in the *International Cosmetic Ingredient Dictionary and Handbook.*

Other data gaps/uncertainties exist regarding use and concentration. In some cases, uses were reported under the VCRP, but no current use concentrations were available; e.g., Methylcellulose in suntan gels. In other cases, use concentrations were reported in the industry survey, but no uses were reported under the VCRP; e.g., Cellulose Gum in permanent waves.

Carboxymethyl Cellulose Acetate Butyrate

No uses of this ingredient were reported to the VCRP (FDA 2009), but an industry survey did report a use concentration of 13% in nail polish (Council 2009).

Carboxymethyl Hydroxyethylcellulose

There were 3 uses of Carboxymethyl Hydroxyethylcellulose reported to the VCRP in 2009 (FDA 2009). An industry survey did not report any use concentrations (Council 2009).

Cellulose

There were 139 uses of Cellulose reported to the VCRP in 2009, with the largest number (125) in lipsticks (FDA 2009). An industry survey reported current use concentrations from 0.002 to 99%, with the highest concentration in makeup preparations (Council 2009).

Cellulose Acetate

There were 9 uses of Cellulose Acetate reported to the VCRP in 2009, all in eye shadows (FDA 2009). Current use concentrations ranged from 0.01 - 5%, with the highest concentration found in foundations and suntan preparations, as reported in an industry survey (Council 2009).

Cellulose Acetate Butyrate

There were 25 uses of Cellulose Acetate Butyrate in nail care products reported to the VCRP in 2009 (FDA 2009). Current use concentrations were reported in an industry survey in a wide range of product categories at concentrations ranging from 0.003 - 17%, with the highest concentration in nail care products (Council 2009).

Cellulose Acetate Propionate

No uses of this ingredient were reported to the VCRP (FDA 2009), but an industry survey did report a use concentration of 13% in nail polish (Council 2009).

Cellulose Gum

Current uses (FDA 2009) of Cellulose Gum reported in the VCRP total 354, with the largest uses in foundations (71) and makeup bases (53). Current use concentrations range from 0.0002 - 20%, with the highest concentration in oral hygiene products (Council 2009).

Cetyl Hydroxyethylcellulose

There were 58 uses of Cetyl Hydroxyethylcellulose reported to the VCRP in 2009 (FDA 2009). Current use concentrations ranging from 0.003 to 2% were reported in an industry survey (Council 2009).

Ethylcellulose

There were 59 uses of Ethylcellulose reported to the VCRP in 2006, with the largest number (22) in skin cleansers (FDA 2006). Current use concentrations ranging from 0.0001 to 4% were reported in an industry survey, with the maximum use concentration used in skin cleansers (Council 2009).

Hydroxyethylcellulose

Current uses (FDA 2006) of Hydroxyethylcellulose reported in the VCRP total 1360, with the largest number of uses in hair conditioners (261) and hair dyes and colors (194). Current use concentrations range from 0.0002 - 39% (Council 2009).

Hydroxyethyl Ethylcellulose

There were 21 uses of Hydroxyethyl Ethylcellulose reported to the VCRP in 2009 (FDA 2009). There were use concentrations ranging from 3% reported for mascara down to 0.3% for a hair conditioner in an industry survey (Council 2009).

Hydroxypropylcellulose

Current uses (FDA 2009) of Hydroxypropylcellulose reported in the VCRP total 97, with the largest uses in "other" shaving preparations. No current use concentrations were reported in an industry survey (Council 2009).

Hydroxypropyl Methylcellulose

Current uses (FDA 2009) of Hydroxypropyl Methylcellulose reported in the VCRP total 301, with the largest uses in bath soaps and detergents. Current use concentrations range from 0.0007 to 36% (Council 2009).

Methylcellulose

Current uses (FDA 2009) of Methylcellulose reported in the VCRP total 55, with the largest uses in skin care preparations (12). Current use concentrations range from 0.004 to 20%, with the highest concentration in the bubble bath category (Council 2009).

Microcrystalline Cellulose

There were 30 uses of Microcrystalline Cellulose reported to the VCRP in 2009 (FDA 2009). In an industry survey, current use concentrations ranged from 0.0001 to 57% (Council 2009).

Table 4. Current uses and use concentrations of Cellulose and Modified Cellulose Polymers.

Product Category	2009 uses (FDA 2009)	2009 concentration (CTFA 2009)
Carboxymethyl Cellulose Acetate Butyrate		
Nail Care Products		
Polish and enamel	-	13%
Total uses/ranges for Carboxymethyl Cellulose Acetate Butyrate	**-**	**13%**
Carboxymethyl Hydroxyethylcellulose		
Hair Coloring Products		
Bleaches	1	-
Skin Care Products		
Cleansers	1	-
Face and neck creams, lotions, etc.	1	-
Total uses/ranges for Carboxymethyl Hydroxyethylcellulose	**3**	**-**
Cellulose		
Bath Preparations		
Soaps and detergents	3	8%
Bath oils, tablets and salts	-	44%
Other bath preparations	-	0.003%
Eye Makeup Preparations		
Eyeliners	12	0.03% - 0.1%
Eye shadow	6	3% - 5%
Eye lotions	2	5%
Mascara	7	0.2% - 5%
Other eye makeup preparations	2	-
Fragrance Preparations		
Colognes and toilet waters	-	0.1%
Perfumes	-	-
Powders	-	0.1%
Non-coloring Hair Preparations		
Aerosol fixatives	-	0.3%
Tonics, dressings, etc.	2	-
Makeup Preparations		
Blushers	-	3%
Face powders	3	2% - 12%
Foundations	2	2% - 8%
Makeup bases	3	1%
Lipsticks	22	0.3% - 5%
Rouges	9	-
Makeup fixatives	1	-
Other makeup preparations	4	0.1% - 99%
Nail Care Products		
Polish and enamel	1	-
Creams and lotions	-	0.1%
Other manicuring preparations	-	0.06%

Table 4 (continued). Current uses and use concentrations of Cellulose and Modified Cellulose Polymers.

Product Category	2009 uses (FDA 2009)	2009 concentration (CTFA 2009)
	Cellulose (continued)	
Oral Hygiene Products		
Other oral hygiene products	-	0.4%
Personal Hygiene Products		
Other personal cleanliness products	2	2%
Shaving Preparations		
Preshave lotions (all types)	-	2%
Other shaving preparations	1	-
Skin Care Preparations		
Cleansers	21	0.02% - 10%
Face and neck creams, lotions, etc.	9	0.002% - 10%
Body and hand creams, lotions, etc.	6	0.002% - 8%
Moisturizers	1	2%
Foot powders and sprays	1	5%
Night creams, lotions, etc.	4	-
Paste masks/mud packs	4	-
Other skin care preparations	9	-
Suntan Preparations		
Suntan preparations		
Suntan gels, creams and liquids	-	2%
Indoor tanning preparations	2	-
Total uses/ranges for Cellulose	**137**	**0.002% - 99%**
	Cellulose Acetate	
Eye Makeup Preparations		
Eye shadow	9	-
Mascara	-	0.1%
Makeup		
Foundations	-	2% - 5%
Makeup bases	-	1%
Skin care products		
Cleansers	-	0.09%
Face and neck creams, lotions and powders	-	0.01%
Suntan Preparations		
Suntan gels, creams and liquids	-	0.01% - 5%
Total uses/ranges for Cellulose Acetate	**9**	**0.01% - 5%**
	Cellulose Acetate Butyrate	
Eye Makeup Preparations		
Eye lotion	-	0.003%
Other eye makeup preparations	1	-
Makeup		
Foundations	-	0.02%
Leg and body paints	1	-
Other makeup preparations	-	10%
Nail Care Products		
Base coats and undercoats	5	-
Extenders	1	-
Nail creams and lotions	-	15%
Polishes and enamels	10	0.04% - 13%
Other manicuring preparations	3	12% - 17% [a]
Skin Care Products		
Moisturizers	3	0.04%
Night creams, lotions, etc.	1	0.02%
Total uses/ranges for Cellulose Acetate Butyrate	**25**	**0.003% - 17%**

Table 4 (continued). Current uses and use concentrations of Cellulose and Modified Cellulose Polymers.

Product Category	2009 uses (FDA 2009)	2009 concentration (CTFA 2009)
	Cellulose Acetate Propionate	
Other manicuring preparations	-	13%
Total uses/ranges for Cellulose Acetate Propionate	**-**	**13%**
	Cellulose Gum	
Baby Products		
Shampoos	-	0.6%
Bath Preparations		
Oils, tablets and salts	3	-
Soaps and detergents	-	0.0008% - 1%
Other bath preparations	-	0.4%
Eye Makeup Preparations		
Eyebrow pencils	1	0.2% - 2%
Eyeliners	12	0.2% - 2%
Eye shadow	18	0.1% - 2%
Eye lotions	6	0.1% - 3%
Eye makeup remover	2	0.0002% - 1%
Mascara	19	0.07% - 3%
Other eye makeup preparations	17	0.5% - 0.7% [b]
Fragrance Preparations		
Other fragrance preparations	2	-
Non-coloring Hair Preparations		
Hair conditioners	2	-
Shampoos	1	0.006% - 0.5%
Hair tonics, dressings, etc.	-	0.6%
Other non-coloring hair preparations	1	-
Hair Coloring Preparations		
Hair dyes and colors	2	0.2% - 8%
Tints	-	0.4%
Rinses	1	-
Bleaches	1	4% (2% after dilution)
Makeup Preparations		
Blushers	2	0.2% - 2%
Face powders	1	0.2% - 10%
Foundations	71	0.2% - 2%
Leg and body paints	3	0.8%
Lipsticks	1	0.1% - 0.3%
Makeup bases	53	0.4%
Rouges	-	0.6% - 0.9%
Makeup fixatives	2	4%
Other makeup preparations	6	0.003% - 0.2%
Nail Care Products		
Nail creams and lotions	-	0.1%
Other manicuring preparations	-	1% - 5% [c]
Oral Hygiene Products		
Dentifrices	8	0.3% - 3%
Mouthwashes and breath fresheners	1	-
Other oral hygiene products	4	20%
Personal Hygiene Products		
Other personal hygiene products	1	-
Shaving Preparations		
Shaving cream	-	1%
Shaving soap	-	1%

Table 4 (continued). Current uses and use concentrations of Cellulose and Modified Cellulose Polymers.

Product Category	2009 uses (FDA 2009)	2009 concentration (CTFA 2009)
Cellulose Gum (continued)		
Skin Care Preparations		
Cleansers	9	0.1% - 2%
Face and neck creams, lotions, etc.	22	0.1% - 3%
Body and hand creams, lotions, etc.	19	0.2% - 0.8%
Moisturizers	22	0.2% - 0.3%
Night creams, lotions, etc.	1	0.1%
Paste masks/mud packs	19	0.2% - 4%
Skin fresheners	4	4%
Other skin care preparations	10	0.6% - 5%
Suntan Preparations		
Suntan gels, creams and liquids	2	0.1% - 0.3%
Indoor tanning preparations	5	0.1%
Other suntan preparations	-	2%
Total uses/ranges for Cellulose Gum	**354**	**0.0002%-20%**
Cetyl Hydroxyethylcellulose		
Eye makeup		
Eye shadow	1	0.003%
Eye lotions	3	0.003%
Noncoloring hair care products		
Conditioners	3	0.2% - 0.3%
Tonics, dressings, etc.	2	0.06%
Other noncoloring hair care products	1	-
Hair coloring products		
Rinses	5	-
Dyes and colors	-	0.6% (0.3% after dilution)
Bleaches	-	2% (1% after dilution)
Cetyl Hydroxyethylcellulose (continued)		
Makeup		
Foundations	-	0.3%
Personal Hygiene Products		
Other personal hygiene products	1	0.4%-1%
Shaving products		
Shaving cream	1	-
Other shaving preparations	-	0.2%
Skin care products		
Cleansers	5	0.1% - 0.2%
Face and neck creams, lotions, etc.	6	0.4%
Body and hand creams, lotions, etc.	3	0.008% - 0.3%
Foot powders and sprays	-	0.05%
Moisturizers	5	0.2% - 0.3%
Night creams, lotions, etc.	1	-
Paste masks/mud packs	2	0.2%
Fresheners	1	-
Other skin care products	6	0.5% - 2%
Suntan products		
Suntan gels, creams, liquids and sprays	6	0.2% - 0.3%
Indoor tanning preparations	6	0.3%
Other suntan preparations	-	0.3% - 0.6%
Total uses/ranges for Cetyl Hydroxyethylcellulose	**58**	**0.003% - 2%**

Table 4 (continued). Current uses and use concentrations of Cellulose and Modified Cellulose Polymers.

Product Category	2009 uses (FDA 2009)	2009 concentration (CTFA 2009)
	Ethylcellulose	
Bath Preparations		
Soaps and detergents	-	0.003% - 0.2%
Eye Makeup Preparations		
Mascara	3	-
Eyebrow pencil	-	2%
Non-coloring Hair Preparations		
Rinses	-	0.4%
Hair Coloring Preparations		
Hair dyes and colors	-	0.4%
Makeup Preparations		
Foundations	1	0.09%
Lipsticks	15	6% - 8%
Other makeup preparations	3	2%
Nail Care Products		
Polishes and enamels	1	0.9%
Basecoats and undercoats	-	0.0001%
Personal Hygiene Products		
Other personal hygiene products	1	-
Shaving Preparations		
Shaving cream	-	0.4%
Shaving soap	-	0.4%
Skin Care Preparations		
Cleansers	17	-
Face and neck creams, lotions, etc.	2	0.02%
Body and hand creams, lotions, etc.	4	0.02%
Moisturizers	-	0.004%
Night creams, lotions, etc.	-	0.2%
Paste masks/mud packs	1	4%
Other skin care preparations	11	0.09% [d]
Suntan Preparations		
Suntan gels, creams and liquids	-	0.8%
Other suntan preparations	-	0.4%
Total uses/ranges for Ethylcellulose	**59**	**0.0001%-8%**
	Hydroxyethylcellulose	
Baby Products		
Lotions, oils, powders and creams	1	-
Other baby products	-	2%
Bath Preparations		
Bath oils, salts, etc.	2	-
Bubble baths	2	0.4%
Soaps and detergents	4	0.004% - 39%
Other bath preparations	1	20%
Eye Makeup Preparations		
Eyebrow pencils	1	0.3% - 1%
Eyeliners	11	0.8% - 1%
Eye shadow	7	0.7%
Eye lotions	12	0.03% - 0.5%
Eye makeup remover	4	-
Mascara	184	0.1% - 2%
Other eye makeup preparations	13	0.2% - 0.3% [c]

Table 4 (continued). Current uses and use concentrations of Cellulose and Modified Cellulose Polymers.

Product Category	2009 uses (FDA 2009)	2009 concentration (CTFA 2009)
	Hydroxyethylcellulose(continued)	
Fragrance Preparations		
Perfumes	9	0.5%
Other fragrance preparations	2	2% [f]
Non-coloring Hair Preparations		
Hair conditioners	261	0.2 - 3%
Hair sprays/aerosol fixatives	1	0.3%
Hair Straighteners	3	-
Permanent waves	-	0.2% - 0.6%
Rinses	3	0.5% - 2%
Shampoos	13	0.3%- 0.5%
Hair tonics, dressings, etc.	83	0.02% - 3%
Wave sets	3	-
Other non-coloring hair preparations	45	0.003% - 1%
Hair Coloring Preparations		
Hair dyes and colors	194	0.2% - 2%
Tints	-	0.7%
Rinses	29	0.4% - 2%
Lighteners with color	3	3%
Bleaches	15	4% (2% after dilution)
Other hair coloring preparations	3	0.8%
Makeup Preparations		
Face powders	-	0.4%
Foundations	4	0.2% - 2%
Lipsticks	5	0.0002% - 7%
Makeup bases	1	0.1%
Other makeup preparations	5	0.2% - 2%
Nail Care Products		
Cuticle softeners	2	1% - 2%
Other nail care products	1	1% - 25%
Oral Hygiene Products		
Dentifrices	3	0.5% - 2%
Mouthwashes and breath fresheners	-	0.3%
Other oral hygiene products	2	-
Personal Hygiene Products		
Underarm deodorants	6	0.04% - 1%
Feminine hygiene deodorants	1	0.8%
Other personal hygiene products	9	0.2% - 1% [g]
Shaving Preparations		
Aftershave lotions	1	0.005%
Shaving cream	21	0.3% - 1%
Shaving soap	-	0.4%
Other shaving preparations	38	0.01% - 1%
Skin Care Preparations		
Cleansers	41	0.1% - 2%
Face and neck creams, lotions, etc.	85	0.2% - 2%
Body and hand creams, lotions, etc.	53	0.04% - 0.6%
Body and hand sprays	-	0.2%
Foot powders and sprays	1	0.1%
Moisturizers	76	0.05% - 0.5%
Night creams, lotions, etc.	16	-
Paste masks/mud packs	11	0.008% - 2%
Fresheners	2	0.06% - 0.1%
Other skin care preparations	59	0.02% - 2%

Table 4 (continued). Current uses and use concentrations of Cellulose and Modified Cellulose Polymers.

Product Category	2009 uses (FDA 2009)	2009 concentration (CTFA 2009)
	Hydroxyethylcellulose(continued)	
Suntan Preparations		
Suntan gels, creams and liquids	-	0.01%-0.4%
Indoor tanning preparations	6	0.09%
Other suntan preparations	2	0.3% - 6%
Total uses/ranges for Hydroxyethylcellulose	**1360**	**0.0002% - 39%**
	Hydroxyethyl Ethylcellulose	
Eye Makeup Preparations		
Mascara	-	3%
Other eye makeup preparations	-	3%
Non-coloring Hair Preparations		
Hair conditioners	4	0.3%
Tonics, dressings, etc.	3	1%
Hair Coloring Preparations		
Bleaches	1	
Makeup		
Other makeup preparations	1	
Skin Care Preparations		
Cleansers	2	
Face and neck creams, lotions, etc.	2	
Body and hand creams, lotions, etc.	2	
Moisturizers	1	
Paste masks/mud packs	1	
Other skin care preparations	4	
Total uses/ranges for Hydroxyethyl Ethylcellulose	**21**	**0.3%-3%**
	Hydroxypropylcellulose	
Bath Preparations		
Bath soaps and detergents	2	-
Other bath preparations	1	-
Eye Makeup Preparations		
Eyeliners	4	-
Eye shadow	1	-
Mascara	1	-
Fragrance Preparations		
Colognes and toilet waters	4	-
Perfumes	6	-
Other fragrance preparations[6]	2	-
Non-coloring Hair Preparations		
Hair conditioners	3	-
Shampoos	1	-
Hair tonics, dressings, etc.	2	-
Other non-coloring hair preparations	7	-
Makeup Preparations		
Foundations	2	-
Nail Care Products		
Cuticle softeners	1	-
Oral Hygiene Products		
Other oral hygiene products	1	-
Personal Hygiene Products		
Underarm deodorants	2	-

Table 4 (continued). Current uses and use concentrations of Cellulose and Modified Cellulose Polymers.

Product Category	2009 uses (FDA 2009)	2009 concentration (CTFA 2009)
	Hydroxypropylcellulose (continued)	
Shaving Preparations		
Aftershave lotions	1	-
Shaving cream	5	-
Other shaving preparations	22	-
Skin Care Preparations		
Cleansers	5	-
Face and neck creams, lotions, etc.	5	-
Body and hand creams, lotions, etc.	3	-
Moisturizers	4	-
Paste masks/mud packs	3	-
Other skin care preparations	8	-
Suntan Preparations		
Indoor tanning preparations	1	-
Total uses/ranges for Hydroxyethylcellulose	**97**	**-**
	Hydroxypropyl Methylcellulose	
Baby Products		
Other baby products	2	-
Bath Preparations		
Bubble baths	4	0.2% - 0.7%
Soaps and detergents	51	0.2% - 4%
Other bath preparations	4	0.003% - 0.6%
Eye Makeup Preparations		
Eyebrow pencils	-	0.05%
Eyeliners	-	0.05% - 0.3%
Eye lotions	-	0.2% - 0.4%
Eye makeup remover	-	3%
Mascara	1	0.2% - 0.5%
Other eye makeup preparations	2	-
Fragrance Preparations		
Cologne and toilet waters	-	1%
Other fragrance preparations	1	0.5% - 0.7%
Non-coloring Hair Preparations		
Hair conditioners	6	0.3%
Hair straighteners	-	0.5%
Shampoos	86	0.002%-2%
Hair tonics, dressings, etc.	4	0.1%-0.8%
Other non-coloring hair preparations	2	2%
Hair Coloring Preparations		
Hair dyes and colors	1	1%
Shampoos	7	-
Bleaches	15	-
Other hair coloring preparations	2	-
Makeup Preparations		
Foundations	-	0.05%
Makeup bases	2	0.1%
Other makeup preparations	1	0.8
Nail Care Products		
Other nail care products	1	-
Oral Hygiene Products		
Other oral hygiene products	1	-
Personal Hygiene Products		
Underarm deodorants	-	0.6% - 2%
Other personal hygiene products	16	0.3% [h]

Table 4 (continued). Current uses and use concentrations of Cellulose and Modified Cellulose Polymers.

Product Category	2009 uses (FDA 2009)	2009 concentration (CTFA 2009)
Hydroxypropyl Methylcellulose (continued)		
Shaving Preparations		
Aftershave lotions	1	-
Shaving soap	-	0.1%
Shaving cream	5	0.002% - 0.2%
Other shaving preparations	2	-
Skin Care Preparations		
Cleansers	33	0.002% - 2%
Face and neck creams, lotions, etc.	11	0.002% - 0.5%
Body and hand creams, lotions, etc.	4	0.03-2%
Foot powders and sprays	1	0.08%
Moisturizers	10	0.3% - 33%
Night skin creams, lotions, etc.	4	0.0007% - 36%
Paste masks/mud packs	7	0.2% - 0.6%
Skin fresheners	1	-
Other skin care preparations	9	0.002% - 0.2%
Suntan Preparations		
Indoor tanning preparations	4	0.5%
Total uses/ranges for Hydroxypropl Methylcellulose	**301**	**0.0007%-36%**
Methylcellulose		
Bath Preparations		
Bubble baths	-	48%
Bath soaps and detergents	5	0.006-20
Other bath preparations	-	0.003%
Eye Makeup Preparations		
Eyeliners	6	-
Eye shadow	-	0.7%
Fragrance Preparations		
Other fragrance preparations	3	0.3%
Non-coloring Hair Preparations		
Hair conditioners	-	0.0001%
Shampoos	3	0.0001%
Tonics, dressings, etc.	-	0.0003%
Other non-coloring hair preparations	3	-
Hair Coloring Preparations		
Bleaches	1	-
Makeup Preparations		
Lipsticks	-	0.07%
Nail Care Products		
Cuticle softeners	1	-
Creams and lotions	1	-
Personal Hygiene Products		
Underarm deodorants	-	0.8%
Other personal hygiene products	-	0.7%
Skin Care Preparations		
Cleansers	10	0.3%
Face and neck creams, lotions, etc.	1	0.03%
Body and hand creams, lotions, etc.	2	0.008% - 0.02%
Moisturizers	2	-
Paste masks/mud packs	5	0.005% - 0.006%
Other skin care preparations	12	-
Total uses/ranges for Methylcellulose	**55**	**0.0001%-48%**

Table 4 (continued). Current uses and use concentrations of Cellulose and Modified Cellulose Polymers.

Product Category	2009 uses (FDA 2009)	2009 concentration (CTFA 2009)
	Methyl Hydroxyethylcellulose	
Nail Care Products		
Other nail care products	-	2%
Total uses/ranges for Methyl Hydroxyethylcellulose	-	**2%**
	Microcrystalline Cellulose	
Bath products		
Soaps and detergents	-	3% - 19%
Other bath preparations	-	0.6%
Eye makeup		
Eyeliner	1	-
Eye shadow	2	2% - 5%
Eye lotion	1	-
Mascara	2	1%
Other eye makeup	1	3% [i]
Fragrance products		
Powders	2	-
Noncoloring hair care products		
Hair conditioners	-	7%
Makeup		
Blushers	-	5%
Foundations	1	0.9 - 25%
Other makeup preparations	1	0.03% - 9%
Oral hygiene products		
Dentifrices	-	0.7%
Other oral hygiene products	1	-
Skin care products		
Cleansers	7	0.06% - 7%
Face and neck creams, lotions, etc.	-	11%
Body and hand creams, lotions, etc.	2	0.2% - 16%
Moisturizers	3	19%
Paste masks/mud packs	2	0.0001% - 57%
Fresheners	2	-
Other skin care preparations	1	0.0001% - 0.5%
Suntan products		
Suntan gels, creams and liquids	-	0.3% - 2%
Indoor tanning preparations	1	-
Other	-	0.8%
Total uses/ranges for Microcrystalline Cellulose	**30**	**0.0001% - 57%**

[a] 12% in a drying enhancer; 13% in a nail topcoat
[b] 0.5% in an eye makeup fixative
[c] 2% - 3% in nail pencil/crayon
[d] 0.09% in a lip moisturizer
[e] 0.2% in a false eye lash glue; 0.3% in a lash primer
[f] 2% in a fragrance gel
[g] 0.2% in a body scrub
[h] shower gel
[i] 3% in an eye makeup fixative

Cosmetic Aerosols

Jensen and O'Brien (1993) reviewed the potential adverse effects of inhaled aerosols, which depend on the specific chemical species, the concentration, the duration of the exposure, and the site of deposition within the respiratory system.

The aerosol properties associated with the location of deposition in the respiratory system are particle size and density. The parameter most closely associated with this regional deposition is the aerodynamic diameter, $\mathbf{d_a}$, defined as the diameter of a sphere of unit density possessing the same terminal setting velocity as the particle in question. These authors reported a mean aerodynamic diameter of 4.25 ± 1.5 µm for respirable particles that could result in lung exposure (Jensen and O'Brien 1993).

Bower (1999), reported diameters of anhydrous hair spray particles of 60 - 80 µm and pump hair sprays with particle diameters of ≥80 µm. Johnsen (2004) reported that the mean particle diameter is around 38 µm in a typical aerosol spray. In practice, he stated that aerosols should have at least 99% of particle diameters in the 10 - 110 µm range.

Non-cosmetic

According to Fitzpatrick et al. (2006), modified celluloses have various uses, such as: thin films, thickeners, binders, and emulsifiers in the food, cosmetic, construction, paint, and oil industries. In pharmaceuticals, they have a well-established use of excipients (i.e., neutral carriers for the delivery of active drug substances to the body). They are found in tablet preparations,

film coatings, and liquid or semi-solid formulations.

Hydroxyethylcellulose

Hydroxyethylcellulose 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. Hydroxyethylcellulose 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 (Lilly and Lowbury 1971).

In the pharmaceutical industry, Hydroxyethylcellulose 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, Hydroxyethylcellulose 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 (Lerk et al. 1978).

In the medical field, Hydroxyethylcellulose 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.

Hydroxyethylcellulose 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 (Fey and Ring 1976).

Hydroxyethylcellulose is used in pastes and sponge substitutes to provide enamel protection and in film-forming compositions for the removal of nicotine tar from teeth. Hydroxyethylcellulose is used as a thickening and film-forming agent in a composition for the prevention of bovine mastitis. Hydroxyethylcellulose is also used as a viscosity controller, film-coating polymer, and suspending agent in various diagnostic techniques (Lion Corporation 1980).

Hydroxyethylcellulose 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) (Code of Federal Regulations 2009).

The U.S. Department of Health and Human Services AIDS Info division (2006) reported that Hydroxyethylcellulose is used in microbicides that are being studied to prevent sexual transmission of HIV. Alone, Hydroxyethylcellulose is often used as a placebo, or control, in studies of microbicides against HIV.

Hydroxypropylcellulose

Hydroxypropylcellulose 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 (Windholz 1983).

Hydroxypropylcellulose is also used as a binder in ceramics and glazes, in vacuum-formed containers and blow-molded bottles, and as a suspending agent in PVC polymerization. Hydroxypropylcellulose 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 (CFR 2009). As an indirect food additive (IFA), Hydroxypropylcellulose is used as a basic component of food contact surfaces (CFR 2009).

Methylcellulose and Hydroxypropyl Methylcellulose

Methylcellulose and Hydroxypropyl Methylcellulose 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 Methylcellulose was safe in the amounts usually taken orally (2 g/day) in antacid products but that insufficient data existed to prove its effectiveness (FDA 1974). Subsequently, no data were submitted during the 2-year probationary period, and Methylcellulose is now classified as generally not safe or effective for antacid use (FDA 2009).

Methylcellulose and Hydroxypropyl Methylcellulose are used in agricultural sprays, ceramics, cements, paints, textiles, and papers (Greminger and Savage 1973). Methylcellulose 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 (Rossoff 1974).

Methylcellulose has been approved by FDA as a multiple-purpose GRAS (generally recognized as safe) food substance (CFR 2009). Hydroxypropyl Methylcellulose is approved as a DFA when used in accordance with GMPs (CFR 2009). Both of these ingredients are used in foods as emulsifiers, film formers, protective colloids, stabilizers, suspending agents, or thickener (Greminger and Savage 1973; CFR 2009). As IFAs, Hydroxypropyl Methylcellulose and Methylcellulose are used as adhesive components and polymeric coatings in the production, treatment, packaging, transporting, and/or holding of food (CFR 2009); Methylcellulose is also used in paper and paperboards as a defoaming agent (CFR 2009). Methylcellulose was first used in foods in the United States in 1960 (Informatics 1972).

Cellulose Gum

Cellulose Gum 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 (Greminger and Savage 1973). The FDA OTC drug review program concluded that Cellulose Gum was safe in the amounts usually taken orally (3 g/day) in antacid products but that insufficient data existed to prove its effectiveness (FDA 1974). Subsequently, no data were submitted during the 2-year probationary period, and Cellulose Gum is now classified as not safe or effective for antacid use (FDA 2009). Cellulose Gum is used widely in textiles, paper, adhesives, insecticides, paints, ceramics, lithography, and detergents (Klose and Glicksman 1972). It is used in veterinary drugs as a suspending agent. Cellulose Gum has been approved by FDA as a multiple purpose GRAS food additive (CFR 2009). It functions as a stabilizer, protective colloid, bulking agent, and water-retention agent (Klose and Glicksman 1972). Cellulose Gum is also approved as a secondary DFA for specific use in boiler water (CFR 2009) and as an IFA used in adhesives and polymeric coatings for the packaging and transporting of food (CFR 2009). Cellulose Gum was first used in foods in the United States in 1945 (Informatics 1972).

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, 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 Cellulose Gum, although this has been attributed to bacterial action present only in herbivorous animals (Informatics 1972; FASEB 1974). Kitagawa et al. (1976) studied the fate of 14C-Hydroxypropylcellulose (labeled in the hydroxypropyl group)

orally administered to rats. The 14C-Hydroxypropylcellulose and nonradioactive Hydroxypropylcellulose 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 Hydroxypropylcellulose is poorly absorbed from the gastrointestinal tract in the rat.

Another metabolism study was conducted in which 14C-Hydroxypropylcellulose 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 (CTFA 1968).

A distribution study was conducted in rats with 14C-Cellulose Gum. Five male rats received 0.4 g 14C-Cellulose Gum in 18 ml of water by stomach tube; a similar dose of unlabeled Cellulose Gum 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 (CTFA 1955).

Biochemical Effects

Okada and Fletcher (1967) studied the inactivation by radiation of deoxyribonuclease I in aqueous solution with high concentrations of Hydroxyethylcellulose. Inactivation of the enzyme depended on the concentrations of both Hydroxyethylcellulose and the enzyme; however, it was not influenced by the viscosity of the system. Each increase of Hydroxyethylcellulose 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 (Kitagawa and Saito 1978). The effects of Methylcellulose on the absorption of nitrofurantoin administered orally to humans was studied. Methylcellulose (5.0% solution) delayed the absorption and urinary excretion without altering the bioavailability of nitrofurantoin (Informatics 1972; Soci and Parrott 1980). A similar delay in the intestinal absorption of sulfafurazole suspended in Methylcellulose was noted in rats (Marvola et al. 1979). Methylcellulose and Cellulose Gum did not exhibit an inhibitory effect on the intestinal absorption of acetaminophen in rats (Sekikawa et al. 1979).

Phenytoin and hexobarbital hydrophilized with Methylcellulose demonstrated increased gastrointestinal bioavailability both in vitro (tests with treated plugs vs pure drug) and in vivo (study in human volunteers) (Lerk et al. 1979). Oral absorption of acetohexamide and tolbutamide in rats was improved by using capsule formulations containing Methylcellulose and Hydroxypropyl Methylcellulose (Said and Al-Shora 1981).

The ocular pharmacokinetics of pilocarpine-HCI in human eyes were studied using HPMC as a vehicle. The amount of pilocarpine-HCI absorbed increased with increasing concentrations of HPMC (Nagataki and Sugaya 1978).

Dietary fibers, including Cellulose Gum, were studied for their effects on the gastrointestinal absorption of cadmium. Cellulose Gum 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 Cellulose Gum. 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 (Kiyozumi et al. 1982). Cellulose Gum, 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) (Quazi et al. 1983).

Weanling rats fed a basal diet containing 4% amaranth (food Red No. 2) and Cellulose Gum had less growth retardation than those receiving a basal diet with amaranth alone. Cellulose Gum had a moderate protective effect against the toxicity of amaranth (Takeda et al. 1979).

Aspirin and salicylic acid suspended in 1% wt/vol dispersions of Cellulose Gum 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 (Barzegar-Jalali and Richards 1979).

A 1% solution of Carboxymethyl Cellulose 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 intestine were examined microscopically and the incidence and severity of hepatic damage were increased in mice receiving both doxorubicin and Carboxymethyl Cellulose. A significant reduction in hepatic glutathione was noted in mice receiving Carboxymethyl Cellulose and doxorubitin plus Carboxymethyl Cellulose in comparison to the controls and mice receiving doxorubicin alone (Decorti et al. 1983). Carboxymethyl Cellulose also mildly decreased hepatic glutathione concentrations in hamsters (Brooks and Pong 1981).

A 1% (wt/vol) solution of Carboxymethyl Cellulose added to fetal calf serum (15%) stimulated a dissociation of cellular aggregates and an extensive outgrowth of neurites in mouse neuroblastoma cells. Neurite formation increased proportionally with the concentration of Carboxymethyl Cellulose during the first 24 h of incubation, plateauing at 1% Carboxymethyl Cellulose. In rat pheochromocytoma cells, the addition of Carboxymethyl Cellulose in the absence of nerve growth factor (NGF) produced no significant neurite outgrowth; however, cells pretreated with Carboxymethyl Cellulose for 1 day responded to NGF with a more rapid rate of neurite outgrowth than control cells not pretreated with Carboxymethyl Cellulose. The extent of outgrowth in this case was the same. Neither dialysis of Carboxymethyl Cellulose nor batch treatment of culture medium with Carboxymethyl Cellulose prior to incubation enhanced neurite outgrowth. Incubation on Carboxymethyl Cellulose-coated dishes also did not enhance outgrowth. The effects of Carboxymethyl Cellulose were attributed to possible increased cell-substratum adhesion or to changes in cell membrane permeability (Koike and Pfeiffer 1979).

Dissolution enhancement

Hydroxyethylcellulose has increased the dissolution rate of ingested p-aminosalicylic acid tablets (Bustos and Cid 1975) and also accelerated the release rate of chlorpromazine, dioxopromethazine, oxytetracycline, and sulfathiazole from hydrogels (Voight et al. 1978).

Tissue Effects

The efficacy and toxicity of intraocularly administered Methylcellulose 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% Methylcellulose 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 Methylcellulose solution provided only minimal endothelial protection from polymethylmethacrylate intraocular lens surfaces (MacRae et al. 1983).

Physiological Effects

Hydroxyethylcellulose 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 received an iv injection of Evans blue after the administration of Hydroxyethylcellulose; bluing of the ears was used as the indicator of increased vascular permeability. Hydroxyethylcellulose was not associated with an increase in vascular permeability (Richter 1969).

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. Hydroxyethylcellulose 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. Hydroxyethylcellulose was relatively inefficient in reducing vascular wall disturbances due to its lack of efficiency in imparting viscoelastic character to the blood (Mostardi et al. 1976). However, other experimenters have reported that adequate levels of viscoelasticity may exist in Hydroxyethylcellulose at concentrations of 500-700 ppm (Greene and Madan 1974).

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% Hydroxyethylcellulose, respectively. Five humans were also similarly studied. Retinal responses obtained with the 0.2% Hydroxyethylcellulose tear solution increased up to 81% in comparison to the values recorded with the 1.6% solution in both rabbits and humans. The difference in electrical conductivity of the two solutions was correlated with differences in electroretinographic amplitudes and was also time dependent (Declercq 1977).

Aqueous solutions of Hydroxypropylcellulose at concentrations of 0.5 and 1.0% did not cause local anesthesia in the cornea of the 6 rabbits tested (Stang and Boggs 1977). The physiological effects of repeated ip injections of Methylcellulose have been studied in mice (Stang and Boggs 1977) and in rats (Palmer et al. 1953). Stang and Boggs (1977) injected mice i.p. with 0.5 ml of a 2.5% Methylcellulose solution three times weekly for 4 weeks. They found that Methylcellulose 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 Methylcellulose. Changes in the blood cells became fairly steady after 2 weeks of Methylcellulose injection and were not affected by splenectomy. Pfrimmer et al. (1978) also studied the effects on mice after similar injections of Methylcellulose and found that Methylcellulose was still visible in macrophages of the spleen and liver up to 40 weeks later. Twice weekly injections of 2.5% Methylcellulose 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 (Palmer et al. 1953). Renal injury was present in rats administered 10 x 50 mg ip injections of Methylcellulose over a 30-day period (Pfrimmer et al. 1978). Splenectomy in the rat prior to administration of Methylcellulose prevented the development of hematological abnormalities (Palmer et al. 1953).

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

Hoshi et al. (1985) investigated the acute toxicity (in rabbits and rats) of Hydroxypropyl Methylcellulose Acetate/Succinate (HPMCAS). No deaths or behavioral abnormalities were observed with a single oral dose of 2.5 g/kg,.

An acute oral LD_{50} test was conducted on a 50% (wt/vol) solution of Hydroxyethylcellulose in corn oil. Doses of 6,834, 10,250, 15,380, and 23,070 mg/kg were administered by oral intubation to groups of 4 rats. After a 16-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 (CTFA 1975).

In another test for oral toxicity, a single dose of Hydroxyethylcellulose 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 Hydroxyethylcellulose water dispersions. No effects on appetite and growth, no deaths, and no lesions were noted during the 14-day observation period (Smyth et al. 1947).

Low, middle, and high viscosity Hydroxypropylcellulose solutions (aqueous) had oral LD_{50}s > 5 g/kg in mice and rats (Kitigawa et al. 1970). No mortalities resulted when rats were administered Hydroxypropylcellulose in gum arabic solution in as large a dose as possible, considering their gastric capacity. The acute oral LD_{50} was defined as > 15 g/kg Hydroxypropylcellulose (Kitigawa et al. 1976). Similarly, no deaths occurred when Hydroxypropylcellulose was administered as a 10% aqueous solution to rats at an oral dose of 10.2 g/kg (CTFA 1962).

A conditioning polish remover containing 0.7% Hydroxypropylcellulose had an acute oral LD_{50} of 10.1 ml/kg (or 8.2 g/kg) in rats (Stillmeadow 1977) (Table 11).

Hydroxypropylmethylcellulose administered to rats in single oral doses of up to 4 g/kg produced no toxic effects or deaths (Informatics 1972; CTFA 1978) (Table 11).

Carboxymethylcellulose administered to rats, rabbits, and guinea pigs in single oral doses of 5 g/kg produced no toxic effects (Informatics 1972). A cosmetic eye makeup product containing 0.605% Carboxymethylcellulose had an oral LD_{50} > 50 g/kg (Table 11) (CTFA 1971).

Cellulose Gum administered to rats, rabbits, and guinea pigs in single oral doses of 3 g/kg produced no toxic effects or deaths (Informatics 1972; CTFA 1970). Acute oral LD_{50}'s of Cellulose Gum were approximately 27 g/kg in rats and 16 g/kg in guinea pigs (Informatics 1972; CTFA 1945).

The LD_{50}s of various cosmetic products containing 0.3 - 3.0% Cellulose Gum are reported in **Table 5**.

lntraperitoneal

No deaths or toxicity resulted from single ip injections of 2.5 g/kg Hydroxypropylcellulose in male mice (10) and male and female rats (10 of each sex) (Kitagawa et al.1970).

Table 5. Acute Oral Toxicity.

Concentration/vehicle	Animal	No. of Animals	LD_{50} (g/kg)	Comments	Reference
		Carboxymethylcellulose			
in olive oil and aqueous gum arabic	rat rabbit guinea pig	Unspecified Unspecified Unspecified	>5 >5 >5	No toxic effects No toxic effects No toxic effects	Informatics (1972)
0.605% in eye product	rat	10	>50	Two deaths due to mechanical obstruction of intestine at high dose; no toxic effect in others	CTFA (1971)
		Cellulose Gum			
3% in aqueous solution	rat rabbit guinea pig	Unspecified Unspecified Unspecified	>3 >3 >3	No toxic effects No toxic effects No toxic effects	Informatics (1972)
CG 2.5% in aqueous solution	rat	12	>3	Ruffed fur and hypoactivity; no deaths	CTFA (1970)
neat	rat	Unspecified	27	LD_{100} = 40 g/kg; no effect level of 20 g/kg	Informatics (1972)
1 g in 2.5 ml olive oil	rat	40	27	-	CTFA (1945)
neat	Guinea pig	Unspecified	16	LD_0 - 10 g/kg	Informatics (1972)
1 g in 2.5 ml olive oil	Guinea pig	30	16	-	CTFA (1945)
3.0% in wrinkle-smoothing cream	rat	5	>15	No deaths, no toxic effects; considered nontoxic by ingestion	CTFA (1980)
1.1% in medicated lotion	rat	5	>10	No deaths, no toxic effects; considered nontoxic by ingestion	CTFA (1977)
1.0% in paste mask	rat	5	>15	No deaths, no toxic effects; considered nontoxic by ingestion	CTFA (1978)
0.5% in liquid eyeliner	rat	10	>5	No deaths, no toxic effects	Consumer Product Testing (1979)
0.3% in moisturizer	rat	10	>7 ml/kg	No deaths, no toxic effects	CTFA (1978)
		Hydroxyethylcellulose			
50% solution in corn oil	rat	4/group	>23.07	Ruffed fur and hypoactivity; some diarrhea at high dose level	CTFA (1975)
10.9% in aqueous solution	rat	10	>8.7	No toxic effects	Smyth et al. (1947)
		Hydroxypropylcellulose			
in aqueous solution	rat mouse	60 30	>5 >5	Light ataxia and inactivity on first day only; no deaths	Smyth et al. (1947)
in gum arabic solution	rat	30	>15	No deaths	Kitagawa et al. (1976)
10% in aqueous solution	rat	25	>10.2	No deaths; some lassitude on first day	CTFA (1962)
0.7% in conditioning polish remover	rat	40	8.2	-	Stillmeadow (1977)
		Hydroxypropyl Methylcellulose			
neat	rat	11	>4	No toxic effects	Informatics (1972)
5% in aqueous solution	rat	15	>1	No toxic effects	CTFA (1978)

A 5% Methylcellulose solution injected ip into mice (18 groups of 10 males) gave an LD_{50} of 147 ml/kg and an ED_0 of 1.0 ml/kg (Informatics 1972).

Hydroxypropylmethylcellulose injected ip into 138 mice had an approximate LD_{50} of 5 g/kg (Informatics 1972).

Usmanov et al. (156) reported that Carboxymethylcellulose was essentially nontoxic when injected ip into mice. Carboxymethylcellulose particles were found in the pulmonary reticuloendothelial cells 48 h after 6 rats were injected ip with 1 ml of a 1.6% Cellulose Gum solution (Informatics 1972).

Intravenous

No deaths or other toxic effects resulted when Hydroxypropylcellulose 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 (Kitagawa et al. 1970). Rabbits injected iv with 10 mg/kg MC developed leukopenia; however, injections of 10-100 ml/kg of a 1% Methylcellulose solution had no effect on blood pressure or respiration (Informatics 1972). 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 Methylcellulose or 50 ml (divided into three injections) of a 0.5% (wt/vol) saline solution of Methylcellulose (Lautsch et al. 1958).

Hueper (1942) reported that iv injections (doses not specified) of Methylcellulose administered to dogs and rabbits caused hematological alterations and retention and accumulation of Methylcellulose in the liver, spleen, lymph nodes, kidney, and vascular walls. He also found that single iv doses of Carboxymethylcellulose caused only mild transitory shifts in the cellular elements of the blood of the treated dogs (Hueper 1945).

Usmanov et aI. (1982) reported that the iv toxicity of Caboxymethylcellulose 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.(1982) reported that Carboxymethylcellulose was essentially nontoxic to mice when injected subcutaneously.

Inhalation

An acute inhalation study was conducted on Hydroxyethylcellulose using 2 rats, 2 mice, and 2 guinea pigs. The animals were exposed to 0.19 mg Hydroxyethylcellulose/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 (CTFA 1974).

Dermal

Hydroxypropylcellulose, 0.8% in an antiperspirant, was tested for dermal toxicity. A single occlusive patch containing 5.0 g/kg of the amount of formulation 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 (CTFA 1977).

Subchronic Toxicity

Oral

Diets containing 0.2, 1.0, and 5.0% Hydroxyethylcellulose 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 Hydroxyethylcellulose were noted (CTFA 1961).

Hydroxypropylcellulose (of low substitution) was administered by stomach tube to groups of 5 male and 5 female rats for 30 days. Hydroxypropylcellulose 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 (Kitagawa et al. 1976).

The oral toxicity of Hydroxypropylcellulose 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 (CTFA 1963).

No adverse effects were noted in chicks fed a diet containing 2% Methylcellulose for 20-21 days (Informatics 1972).

No toxic effects were observed in rats given 0.5 g/kg Methylcellulose (method unspecified) for 4 weeks. Rats ingesting Methylcellulose 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% Methylcellulose diet for 90 days had significant growth depression. This was attributed to the lack of nutrition in a "bulk"-producing diet and not to any toxic effect (Informatics 1972).

Dogs fed up to 100 g Methylcellulose daily for 1 month had no toxic effects (Informatics 1972).

Hydroxypropylmethylcellulose and Methylcellulose 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% Methylcellulose or Hydroxypropylmethylcellulose with a nominal viscosity of 10 cp as well as 0, 3, and 10% Methylcellulose or Hydroxypropylmethylcellulose with a nominal viscosity of 4000 cp. Groups of 2 male and 2 female beagle dogs received diets containing 0, 2, and 6% Hydroxypropyl-methylcellulose 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 component values, organ weights, or gross or microscopic alterations (McCollister et al. 1973).

Hydroxypropylmethylcellulose, in two studies, was fed to rats for 90 days at concentrations 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% Hydroxypropylmethylcellulose diet died of undetermined causes. No lesions were seen in any tissue from these rats (Informatics 1972).

Groups of 20 rats were fed Hydroxypropylmethylcellulose 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 (Informatics 1972).

Rabbits (6 per group) fed Hydroxypropylmethylcellulose 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 (Informatics 1972).

Two dogs were fed 25 or 50 g HPMC daily for 30 days. The dog fed 50 g Hydroxypropylmethylcellulose had weight loss, diarrhea, and anemia. Urinalyses, organ weights, and organs were normal in both dogs (Informatics 1972).

Hydroxypropylmethylcellulose 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% Hydroxypropylmethylcellulose 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 (Schwetz et al.1976).

No adverse effects were noted in chicks fed a diet containing 2% Cellulose Gum for 20 days (Informatics 1972).

No toxic effects were noted in rats fed 0.3 or 0.5 g Cellulose Gum daily for 2 months or in rats fed a diet containing 14% Cellulose Gum for 5 weeks. Rats fed a diet containing either 20% Cellulose Gum or Carboxymethylcellulose for 63 days also had essentially no toxic effects. A slight decrease in growth was observed in the rats receiving 20% Cellulose Gum, although this was attributed to a decrease in nutrient food intake resulting from the bulkiness of the diet (Informatics 1972).

Five dogs were given doses of Cellulose Gum 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 Cellulose Gum into the reticuloendothelial cells of the aorta was observed at microscopic examination (Informatics 1972).

Rats were fed a hypercholesterolemic diet both with and without 5% Carboxymethylcellulose for 8 or 14 days in order to evaluate the hypocholesteroemic effect of Carboxymethylcellulose. Carboxymethylcellulose depressed plasma and liver cholesterol concentrations compared to controls; however, it did not alter cholesterol absorption from the gut (Informatics 1972).

According to Hoshi et al. (1985), the acute toxicity (in rabbits and rats) and the subchronic and chronic toxicities (in rats) of Hydroxypropyl Methylcellulose Acetate/Succinate (HPMCAS), a potentially useful pharmaceutical excipient, were investigated. In the subchronic toxicity study (0.63, 1.25 or 2.5 g/kg daily as a single oral dose in the morning, 6 days per week (not Sunday) for 2 months), no significant behavioral abnormality was observed. There was some decrease in body weight gain in rats of both sexes, but the effect was not statistically significant. 3)In the chronic toxicity study (1.25 or 2.5 g/kg daily as a single oral dose in the morning, 6 days per week (not Sunday) for 6 months), no significant behavioral abnormality was observed. There was some decrease in body weight gain in male rats, but it was not statistically significant. 4)Various biochemical and physiological abnormalities in rats were noted in all groups (including the control groups) in the toxicity studies, but there appeared to be no significant dose-related finding attributable to the administration of HPMCAS.

Kotkoskie and Freeman (1998) reported on a subchronic oral toxicity study of Ethylcellulose aqueous dispersion in the rat. Groups of 20 male and 20 female Sprague-Dawley rats were administered undiluted Ethylcellulose aqueous dispersion by oral gavage at doses of 903, 2709, or 4515 mg/kg body wt/day (dry weight basis) for 90 days. Control animals received water at the same dosage volume as the high-dose group. Body weights and feed consumption were recorded weekly. Blood was collected prior to study termination for hematology and clinical chemistry measurements. Survivors underwent complete necropsies on days 91 - 94. The only treatment-related clinical sign observed were pale feces, which were noted among males and females receiving 2709 and 4515 mg/kg/day Ethylcellulose. No statistically significant differences in body weights, body weight gains, food consumption and organ weights were noted among males and females when compared with controls. No treatment-related effects in hematology parameters were noted. Significantly decreased total protein and globulin levels and increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in male rats receiving 2709 and 4515 mg Ethylcellulose/kg/day were considered to be treatment related. No gross or microscopic lesions were attributed to Ethylcellulose treatment. Under the conditions of this study, the no-observed-adverse-effect level (NOAEL), for female rats were in excess of 4515 g/kg/day; the NOAEL) for male rats was 903 mg/kg/day.

DeMerlis et al. (2005) reported on a subchronic toxicity study in rats with an aqueous Ethylcellulose dispersion. A study was conducted to assess the toxicity of spray-dried Ethylcellulose when orally administered, via dietary admixture, to Sprague-Dawley CD rats (20/sex/group) at dose levels of 0, 2000, 3500, and 5000 mg/kg/day for a period of at least 3 months. After 3 months of treatment, all rats scheduled for termination were killed and selected organs were weighed. Complete macroscopic examinations and histopathological evaluation of selected tissues were conducted on all animals. Neuropathological examinations were performed on 5 animals/sex/group. No mortality occurred during the study. Clinical observations, ophthamology, body weight and food consumption, hematology, coagulation, clinical chemistry, urinalysis, functional observational assessments, motor activity, organ weights and ratios, and macroscopic and microscopic observations did not reveal any significant, consistent, dose-dependent test article-related adverse effects. The NOAEL was 5000 mg/kg/day, the highest dose tested.

Hydroxypropylcellulose 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. Hydroxypropylcellulose 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 (Kitagawa et al. 1976).

In studies conducted prior to 1973, no toxic effects were noted in rats fed up to 5.0% Methylcellulose for 184 days or in rats fed 1.8% Methylcellulose for 8 months (Informatics 1972).

Methylcellulose 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% Methylcellulose 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 component values, organ weights, gross and microscopic examinations, or in tumor incidence (McCollister et al. 1973). In studies conducted prior to 1973, rats were fed diets containing up to 30% Hydroxypropyl-methylcellulose for periods up to 2 years. No significant toxic effects were noted other than growth retardation at concentrations of Hydroxypropylmethylcellulose 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 Hydroxypropylmethylcellulose also showed no toxic effects (Informatics 1972). In studies conducted prior to 1973, rats and mice were fed diets containing 0 and 5% Carboxymethylcellulose for periods of 8 months-1 year (rats) and from weaning to death (mice). No toxic effects were noted (Informatics 1972).

Cellulose Gum 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 Cellulose Gum 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% Cellulose Gum for 8 months; no toxic effects were noted. In another study, rats and mice were fed diets containing 0, 1, and 10% Cellulose Gum for 104 and 100 weeks, respectively. Deaths in the first 1 1/2 years were due to pulmonary infection; later deaths were attributed to neoplasms common to aging rats and mice. There was no indication of Carboxymethylcellulose absorption or storage. Tumor frequencies were normal. A retardation in growth was observed in the rats receiving 10% Cellulose Gum, although it was noted that these rats also had a higher feed intake

(Informatics 1972).

In unpublished studies, Cellulose Gum was evaluated for oral toxicity in dogs, guinea pigs, and rats. Diets containing 2, 5, 10, and 20% Cellulose Gum 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 (CTFA 1951).

Groups of 20 guinea pigs were fed diets containing 0 (15 guinea pigs only), 0.5, and 1.0 g/kg Cellulose Gum for 1 year. No effects were noted in growth or at necropsy (CTFA 1947).

Groups of 25 rats (males and females) were fed diets containing 0, 0.1, 0.5, and 1.0 g/kg Cellulose Gum 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 (CTFA 1947).

Intravenous

Hydroxyethylcellulose (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 Hydroxyethylcellulose solution for 6-12 weeks. Concentrations of Hydroxyethylcellulose 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. Hydroxyethylcellulose 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 (Hueper 1946).

Hueper (1946) found that repeated iv doses (doses not specified) of Carboxymethylcellulose to dogs resulted in a decrease in blood hemoglobin and an increase in sedimentation rate. Carboxymethylcellulose was stored in Kupffer cells, reticular cells of the spleen, endothelial cells of the glomeruli, and on the walls of the aorta and its branches.

Dermal

A wrinkle smoother product containing 3.0% Cellulose Gum 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 (CTFA 1981).

A lotion containing 1.1% Cellulose Gum 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 (CTFA 1978).

Chronic Oral Toxicity

A 2-year chronic oral toxicity test was conducted by Smyth et al. (1947) in which groups of 32 Wistar strain rats, 16 males and 16 females, each received diets containing 0.2, 1, or 5% Hydroxyethylcellulose. 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 Hydroxyethylcellulose. Criteria evaluated included growth, feed 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 feed intake of the rats fed the 5% Hydroxyethylcellulose 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 (Smyth et al 1947).

Ocular Irritation

Hydroxyethylcellulose 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% Hydroxyethylcellulose was instilled into each rabbit eye. A dose of 0.1 ml of a 2% (wt/vol) solution of Hydroxyethylcellulose 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% Hydroxyethylcellulose were 4.0 and 10.0, respectively; means at all subsequent readings were 0. Those rabbits receiving 2% (wt/vol) Hydroxyethylcellulose 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, Hydroxyethylcellulose was initially minimally irritating to rabbit eyes; however, all irritation had cleared by 24 h (CTFA 1975).

Laillier et al.(1976) 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 Hydroxyethylcellulose 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% Hydroxyethylcellulose had no significant effect on the eyes; 1% Hydroxyethylcellulose was one

of the lowest ranking compounds causing some irritation. Following repeated administration, both Hydroxyethylcellulose 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% Hydroxyethylcellulose, increase in µg Evans blue/ml aqueous humor after 3, 7, and 13 instillations of 0.5% Hydroxyethylcellulose, increase in µg Evans blue/ml aqueous humor after 1 instillation of 1.0% Hydroxyethylcellulose, increase in µg Evans blue/g dry weight of conjunctivae after 3, 6, and 13 instillations of 1.0% Hydroxyethylcellulose, and a decrease in percent dry weight of conjunctivae after 3 administrations of 1.0% Hydroxyethylcellulose (Laillier et al. 1976).

An ocular irritation test was conducted on Hydroxyethylcellulose (2%; two samples), Hydroxypropylcellulose (2%), Methylcellulose (2%; three samples), and Cellulose Gum (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) were calculated for each sample. The AOIls ranged from 5.33 to 10.50 (max = 110). No lesions of the ocular mucous membrane were noted. The investigators concluded that Hydroxyethylcellulose, Hydroxypropylcellulose, Methylcellulose, and Cellulose Gum, under these conditions, were slightly irritating (Guillot et al. 1981).

The Draize method was also used to evaluate the irritancy of 0.5 and 1.0% aqueous solutions of Hydroxypropylcellulose 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 Hydroxypropylcellulose solution was 0; the positive control had a score of 22.7. Hydroxypropylcellulose was considered nonirritating (Kitagawa and Saito 1978).

A 5 mg Hydroxypropylcellulose-soluble ocular insert was evaluated for irritation in both eyes of 12 Beagle dogs. 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 (Gelatt et al. 1979).

Methylcellulose, in a 1-2% solution, failed to produce irritation to the conjunctival membrane of a rabbit (Informatics 1972).

A 0.1 mg sample of Hydroxypropylmethylcellulose (solid) was instilled into 1 eye of 1 rabbit for 30-sec. 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 (CTFA 1978).

Cellulose Gum was evaluated for ocular irritancy in 2 Draize tests. A 0.1 mg sample of Cellulose Gum (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= 110) by 3 and 4 days in the first and second tests, respectively (CTFA 1974).

Ocular irritation studies are summarized in **Table 6**.

Hydroxypropylcellulose (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 (CTFA 1962).

Durand-Cavagna et al. (1989) reported on corneal toxicity studies in rabbits and dogs with Hydroxyethylcellulose and benzalkonium chloride. Hydroxyethylcellulose is used as a viscosity-increasing agent in ophthalmic formulations to prolong corneal contact time and increase intraocular drug levels. Fifty-seven male and 57 female HY/CR albino rabbits (Charles River), weighing 2.15 - 3.40 kg, were 3 to 4 months old at the initiation and were used in several studies. Eight male and 8 female purebred Beagle dogs, weighing 7.0 - 9.3 kg, were 7 to 8 months at the start of the study. The animals were randomly assigned into groups of 4 to 6 animals of each sex. The animals received 30 µl of the test material in the conjunctival sac of the left eye (rabbit) or in the left eye (dog) 3 times a day, 3 hrs apart, daily for 14 weeks (rabbits) or 27 weeks (dogs). The right eye was left untreated and served as the control.

Corneal epithelial changes were seen by slit lamp and light microscopic examination in rabbits, but not dogs after multiple instillations of an ophthalmic vehicle containing 0.01% BAK and 0.5% Hydroxyethylcellulose. Microscopically, there was sloughing of superficial epithelial cells and a slight loss of polarity of the basal cells. Formulations with 0.01% BAK and Hydroxyethylcellulose, at concentrations between 0.3% and 0.8%, caused these changes, but these changes were not seen with BAK or Hydroxyethylcellulose alone. The authors therefore concluded that Hydroxyethylcellulose increased the viscosity and prolonged the contact time of BAK with cornea resulting in corneal epithelial damage in the rabbit. Physiological and anatomical features of the rabbit combined with the increased contact time were concluded to favor these changes in this species. The results, according to the authors, confirm that the rabbit is a sensitive and unique species in studies of ocular toxicity of drugs (Durand-Cavagna et al. 1989).

Mucosal Irritation

A moisturizing cream containing 0.3% Cellulose Gum 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 (CTFA 1978).

Dermal Irritation

A primary skin irritation test was conducted on Hydroxyethylcellulose (2%; two samples), Hydroxypropylcellulose (2%), Methylcellulose (2%; three samples), and Cellulose Gum (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). Hydroxyethylcellulose, Hydroxypropylcellulose, Methylcellulose, and Cellulose Gum, under these conditions, were nonirritating (Guillot et al. 1981).

A cutaneous tolerance test also was conducted on this same group of cellulose solutions. Aqueous solutions of 2% Hydroxyethylcellulose (two samples), 2% Hydroxypropylcellulose, 2% Methylcellulose (three samples), and 1, 4, and 10% Cellulose Gum 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

Table 6. Ocular irritation studies using rabbits.

Ingredient	No. of Animals	Assay	Results	Reference
		Carboxymethylcellulose		
0.605% in eye makeup product	6	Single instillation	nonirritating	CTFA (1971)
		Cellulose Gum		
1% in aqueous solution	6	Official French method	slightly irritating	Guillot et al. (1981)
4% in aqueous solution	6		slightly irritating	
10% in aqueous solution	6		slightly irritating	
0.1 mg in aqueous solution	6	Draize	nonirritating	CTFA (1974)
100% (0.01 g)	6	Draize	nonirritating	CTFA (1974)
3.0% in wrinkle-smoothing preparation	6	Modified Draize	minimally irritating	CTFA (1977)
1.1% in a medicated lotion	6	Modified Draize	nonirritating	CTFA (1977)
1.0% in paste mask	6	Modified Draize	nonirritating	CTFA (1978)
0.5% in liquid eyeliner	9 (3 rinsed, 6 unrinsed)	Draize	No ocular reactions; nonirritating with or without rinse	Food and Drug Research Laboratories (1979)
0.3% in moisturizer	6	Single instillation	Slight conjunctival redness noted after 1 h, but clear by 24 h; no effect on corneal and iridial membranes	CTFA (1978)
		Hydroxyethylcellulose		
100% (100 mg)	8 (4 rinsed, 4 unrinsed)	Draize	nonirritating	CTFA (1975)
2% in aqueous solution	8 (4 rinsed, 4 unrinsed)	Draize	nonirritating	CTFA (1975)
0.5 and 1.0% in aqueous solution	8	dry tissue weight and dye diffusion	Low irritancy after single and repeated administration	Laillier et al. (1976)
2% in aqueous solution	6	Official French method	slightly irritating	Guillot et al. (1981)
2% in aqueous solution	6		slightly irritating	
		Hydroxypropylcellulose		
100% (50 mg)	2 - both eyes treated (1 eye rinsed, 1 eye unrinsed in each animal)	Draize	Slight irritation in unrinsed eyes at 1 h all eyes with score of 0 at 24 h	CTFA (1962)
2% in aqueous solution	6	Official French method	slightly irritating	Guillot et al. (1981)
0.5 and 1.0% in aqueous solution	6	Draize	nonirritating	Kitagawa (1978)
5 mg	12	Soluble ocular inserts	Nonirritating	Gelatt et al. (1979)

Table 6 (continued). Ocular irritation studies using rabbits.

Ingredient	No. of Animals	Assay	Results	Reference
		Methylcellulose		
2% in aqueous solution	18	Official French Method	slightly irritating	Guillot et al. (1981)
MC 1-2% solution	1	-	no irritation	Informatics (1972)
		Hydroxypropyl Methylcellulose		
100% (0.1 mg)	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	CTFA (1978)

Hydroxyethylcellulose 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 (Minnesota Mining and MFG. Co. 1980). Teats of cows protected by a similar composition containing Hydroxyethylcellulose after twice daily milking for 8 months also had no signs of irritation (Andrews et al. 1978).

An antiperspirant containing 0.8% of Hydroxypropylcellulose 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. Plls of 0.0 and 0.2 (max = 8) were obtained on the intact and abraded skin, respectively. The product was considered mildly irritating (CTFA 1979).

Hydroxypropylmethylcellulose (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 Hydroxypropyl-methylcellulose, and the other received Hydroxypropyl-methylcellulose moistened with water. Each rabbit additionally received Hydroxypropylmethylcellulose applications daily for 3 days on an abraded skin site. No skin irritation was observed from contact with the dry material. The moistened Hydroxypropylmethylcellulose produced a slight redness believed to be due to the material sticking to the skin. There was no evidence of systemic injury. Solid Hydroxypropylmethylcellulose was essentially nonirritating and not absorbed through the skin in harmful amounts (CTFA 1978).

A facial cleanser containing 1.1% Hydroxypropylmethylcellulose was evaluated for skin irritation using 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) (CTFA 1972).

Application of Cellulose or Carboxymethylcellulose to the shaved abdominal area of rabbits five times per week for 4 weeks produced no signs of skin irritation (Informatics 1972).

Cosmetic products containing from 0.3 to 3.0% Cellulose Gum or Carboxymethylcellulose were found nonirritating to slightly irritating when applied topically to the skin of rabbits.

Dermal Sensitization

Hydroxypropylmethylcellulose was evaluated for sensitization using a 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% Hydroxypropylmethylcellulose in saline, and 0.1 ml of 1% Hydroxypropylmethylcellulose 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% Hydroxypropylmethylcellulose in petrolatum. Following a 2-week rest, a 24-h occlusive challenge patch containing 25% Hydroxypropylmethylcellulose in petrolatum was applied to the shaven flank of each animal. The control guinea pigs also received the challenge application. Reactions were scored 24 and 48 h after patch removal. Hydroxypropylmethylcellulose did not produce any responses indicative of sensitization and was considered a nonsensitizer (CTFA 1980).

Hydroxypropylmethylcellulose was further evaluated for sensitization in Hartley albino guinea pigs. Ten male guinea pigs each received a 0.1 ml application to the clipped back of 2% Hydroxypropylmethylcellulose 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 similarly tested with a positive control. No responses were noted on challenge with Hydroxypropylmethylcellulose, 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 Hydroxypropylmethylcellulose (CTFA 1978).

Phototoxicity

A phototoxicity test was conducted on a mascara containing 0.4% Hydroxyethylcellulose. 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 (CTFA 1979).

A liquid eyeliner containing 0.5% Cellulose Gum 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 (FDRL 1979).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

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% Hydroxyethylcellulose. Reproductive effects were determined on day 19. Fetal resorption was significantly increased by Hydroxyethylcellulose at both concentrations when administered on days 3-7; there were 18.7 and 43.8% resorptions for 1 and 4% Hydroxyethylcellulose, respectively, compared to 8.3% for the saline control and 5.1% for the sesame oil. Weights of the surviving fetuses in the 4% Hydroxyethylcellulose 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% Hydroxyethylcellulose solution, and 1.39 and 8.57% for the sesame oil. All groups receiving the Hydroxyethylcellulose solutions had a lower percentage of fetuses with additional ribs than the saline control (Guettner et al. 1981).

Kitagawa et al. (1978) studied the reproductive effects of Hydroxypropylcellulose in both rabbits and rats. Doses of 0, 200, 1000, and 5000 mg Hydroxypropylcellulose/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.

Hydroxypropylcellulose 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 Hydroxypropylcellulose, 0, 200, 1000, and 5000 mg/kg per day by stomach tube on days 7-17 of gestation. Hydroxypropylcellulose 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 (Kitagawa et al. 1978).

In two separate studies, three generations of rats were fed basal diets containing up to 5% Methylcellulose. 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 (FASEB 1974).

Pregnant rabbits were fed diets containing 0.25-0.5% Methylcellulose on days 9-16 of gestation. No reproductive effects were noted; however, some fetal toxicity was observed (FASEB 1974).

Methylcellulose, in corn oil, was administered by intubation to pregnant mice, rats, and hamsters. Doses of 345 mg/kg Methylcellulose given to mice on days 6-15 of gestation produced no effects on nidation or maternal or fetal survival. Doses of Methylcellulose (1600 mg/kg per day) similarly administered to mice produced no clear evidence of reproductive 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 (FASEB 1974).

The reproductive toxicity of Methylcellulose was studied in CD/1 mice. Groups of 20 pregnant mice were administered Methylcellulose 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}. Methylcellulose 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 (Cannon Labs 1975).

The reproductive toxicity of Methylcellulose was similarly studied in Sprague-Dawley rats. Groups of 20 pregnant rats received Methylcellulose 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}. Methylcellulose 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 (Cannon Labs 1975).

Three generations of rats were fed diets containing 0, 0.1, 0.5, and 1.0 g/kg Cellulose Gum. 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 (Informatics 1972).

Rats fed 5 ml of a 0.2% solution of Caboxymethylcellulose on the eleventh day of gestation showed an increase in resorption rate and in the number of malformed fetuses (FASEB 1974).

Methylcellulose, Cellulose Gum, and Carboxymethylcellulose have been used as vehicles and negative controls in various reproductive studies. Concentrations ranged from 0.5 to 1.25% for Methylcellulose (Horvath et al. 1976; Robertson et al. 1979), 0.5 to 2% for Cellulose Gum (Fritz et al. 1976; Miller and Becker 1976) and 1% for Carboxymethylcellulose (Sullivan and McElhatton 1977).

Gupta et al. (1996) evaluated the reproductive toxicity of alternative vehicles (PEG-400, cremephor, Carboxymethylcellulose) in comparison with Methylcellulose (0.5%). Pregnant Sprague-Dawley rats and New Zealand White rabbits were randomly assigned to 4 dose groups (10/group). The animals were dosed between gestational day 6 - 17 (rats) and 6 - 18 (rabbits) by oral gavage at concentrations of 1 ml/kg (rats) and 2 ml/kg (rabbits) with either 0.5% Methylcellulose, PEG-400, cremephor, or 0.1% Carboxymethylcellulose.

Feed consumption and body weights were recorded daily. Cesarean sections were performed on gestational days 21 and 28 for the rats and rabbits, respectively. Reproductive parameters,

numbers of corpora lutea, implantation sites, and resorptions were recorded and the fetuses were examined for external, visceral and skeletal malformations. In the rabbits, loose stools were noted in the PEG-400, cremephor, and 0.1% Carboxymethylcellulose groups. There were no treatment-related mortalities. Body weights, feed consumption and reproductive parameters were comparable between the groups. Some differences were noted in the incidences of minor anomalies between groups, but none were biologically significant (Gupta et al. 1996).

Hoshi et al. (1985) reported on a fertility study was carried out in Slc: SD rats orally administered Hydroxypropyl Methylcellulose Acetate/Succinate (HPMCAS), a useful pharmaceutical excipient, at dose levels of 625, 1,250 and 2,500 mg/kg/day. Male rats were treated with HPMCAS from 60 days before pairing until the completion of mating. Female rats received HPMCAS for 22 days, from 14 days prior to mating up to Day 7 of gestation. All pregnant females were sacrificed on Day 21 of gestation and all fetuses were examined for abnormalities. No abnormal signs were seen in mating or fertility in the rats treated with HPMCAS. No external, internal and skeletal anomalies attributable to HPMCAS were observed in the fetuses. It was concluded that HPMCAS had no harmful effect on mating, fertilization, implantation, or embryonic development.

Hoshi et al. (1985) also reported on a perinatal and postnatal study was carried out in Slc: SD rats orally administered Hydroxypropyl Methylcellulose Acetate/Succinate (HPMCAS), at dose levels of 625, 1,250 and 2,500 mg/kg/day for a period from day 17 of gestation to day 21 after delivery. All pregnant rats were allowed to litter naturally, and the postnatal development of the offsprings was observed. In the administered group of 2500 mg/kg, the liver weight was significantly increased in males and showed a tendency to increase in females as compared with control. No significant differences between the control group and the administered groups were found in postnatal growth and differentiation, behavior and reproductive ability of male and female offsprings.

A reproductive study was carried out in New Zealand White rabbits in order to examine the teratogenic potentiality of HPMCAS (Hoshi et al. 1985). HPMCAS was orally administered at dose levels of 625, 1,250 and 2,500 mg/kg/day for a period of 13 days from day 6 to day 18 of gestation. All pregnant females were sacrificed on day 29 of gestation and their fetuses were examined. The administration of HPMCAS during a period of organogenesis produced no embryotoxic and teratogenic effects as well as no influence on behavior, appearance and growth of animals.

Palmieri et al. (2000) reported on a developmental toxicity study of Ethylcellulose aqueous dispersion administered orally to rats. Groups of 25 presumed-pregnant Charles River Sprague-Dawley CD rats received doses of 0, 903, 2709, and 4515 mg/kg/day (dry weight basis) of Ethylcellulose administered undiluted once daily via oral gavage on days 6-15 of gestation. All surviving dams underwent Cesearean sectioning on day 20 of gestation. Fetuses were weighed, sacrificed and subject to external, visceral and skeletal evaluations.

No test material-related maternal deaths occurred; 1 high-dose female died on day 14 due to gavage error. The only treatment-related clinical sign noted among dams receiving 2709 mg/kg/day and greater was pale feces, which were attributed to the presence of the test material in the feces. No statistically significant differences were noted among the measured maternal parameters. Fetal sex ratios and body weights were similar in all groups. The results of external and visceral fetal evaluations revealed no treatment-related alterations.

The only statistically significant findings noted during the skeletal evaluation were increased litter incidences of incompletely ossified or wavy ribs noted among fetuses receiving 4515 mg/kg/day, and a significant increase in the litter incidence of thickened ribs at doses of 2709 and 4515 mg/kg/day. Given the nature of these findings and the lack of effects on any other parameter measured in this study, they were not considered by the authors to be adverse effects of treatment. Under the conditions of this study, the authors reported that the maternal and fetal NOAEL was in excess of 4515 mg/kg/day (Palmieri et al. 2000).

Cappon et al. (2003) evaluated the potential for Hydroxypropyl Methylcellulose Acetate/Succinate (HPMCAS) to produce developmental and reproductive toxicity in a series of studies that included rat and rabbit teratology studies, a rat fertility study, and a rat peri- and postnatal study. The authors concluded that there were no compound-related findings.

In the cesarean-section phase of the rat teratology study, however, clubfoot was reported for 0.8, 2.1, 5.5, and 4.1% of fetuses in the control, 625, 1250, and 2500 mg/kg groups, respectively. There were no significant increases in external anomalies, but the apparent dose-related increase in clubfoot was not specifically addressed.

In the rabbit teratology study, the number of litters evaluated (12-13 per group) was not consistent with current regulatory guidelines. Therefore, to definitively establish the potential of HPMCAS to produce developmental toxicity, embryo/fetal development studies were carried out in rats and rabbits.

Groups of 20 pregnant Sprague-Dawley rats and New Zealand White rabbits were dosed with 0, 50, 150, 625, or 2500 mg/kg HPMCAS from gestational day (GD) 6-17 or GD 7-19 for rats and rabbits, respectively. Fetuses were collected by cesarean section and examined for external, visceral and skeletal development. No developmental toxicity was observed as a result of HPMCAS exposure demonstrating that maternal HPMCAS exposure during gestation does not induce developmental anomalies. There were no findings of clubfoot or other limb anomalies in these studies at dose levels equivalent to those that were previously associated with a possible increase in clubfoot. The conclusion of the earlier study indicating that treatment with HPMCAS at doses up to and including 2500 mg/kg did not produce developmental toxicity was confirmed with these studies. The authors stated that it was likely that the clubfoot noted in the earlier rat teratology study was a misdiagnosis or artifact (Cappon et al. 2003).

GENOTOXICITY

Methylcellulose (50 µg) was nonmutagenic in the Ames test with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, both with and without metabolic activation (Blevins and Taylor 1982).

Methylcellulose was evaluated (Litton Bionetics 1974) 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 Methylcellulose 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 Methylcellulose 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 µg/ml Methylcellulose. Methylcellulose was nonmutagenic in the dominant lethal assay in rats dosed with up to 5000 mg/kg (Litton Bionetics 1974).

Cellulose Gum 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 the 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 Cellulose Gum was nonmutagenic (Kawachi et al. 1980).

Carboxymethylcellulose was nonmutagenic in *S. typhimurium* strains TA100 and TA98 both with and without metabolic activation and in Escherichia co/I strain WP-2 without metabolic activation (Sugimura et al. 1976).

DeMerlis et al. (2005) reported on genotoxicity tests with an aqueous Ethylcellulose dispersion. A series of genotoxicity tests were conducted with Ethylcellulose. Ethylcellulose showed no evidence of mutagenic activity in the bacterial reverse mutation test with and without metabolic activation and in the in vitro cell mutation assay under the experimental conditions employed. Ethylcellulose did not show any evidence of causing chromosome damage or bone marrow cell toxicity when administered by gavage in the mouse micronucleus in vivo test procedure. According to the authors, these finding support the safety of Ethylcellulose for use as an excipient. Concentrations were not provided.

CARCINOGENICITY

Twenty-five Bethesda black rats were injected subcutaneously with 500 mg of powdered Methylcellulose and tissues were examined 2 years later. The tumor incidence was similar in treated rats and controls (Informatics 1972).

Several studies have been conducted to evaluate the effects of Methylcellulose on rats transplanted subcutaneously with Murphy-Sturm lymphosarcoma. Intraperitoneal injections of Methylcellulose (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 Methylcellulose (Informatics 1972).

Weekly subcutaneous injections of 1 ml of a 2% Carboxymethylcellulose solution administered to 30 rats for 73 weeks produced fibrosarcomas at the injection site in 43% of the animals. Deposits of Carboxymethylcellulose were found at the injection sites (Informatics 1972).

Carboxymethylcellulose has been used as the vehicle and negative control in a bioassay of selenium sulfide. A 0.5% aqueous solution of Carboxymethylcellulose 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 (National Cancer Institute 1980).

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation/Sensitization

Repeated insult patch tests (RIPTs), single insult patch tests (SIPTs), cumulative irritancy tests, and maximization test have been conducted in clinics using Cellulose Gum, Hydroxyethylcellulose, Hydroxypropylcellulose, Hydroxypropyl Methylcellulose, and Methylcellulose as shown in **Table 7**. Overall, these ingredients are non-irritating and are non-sensitizing.

Photosensitization

RTL (1978) used an RIPT to evaluate the photosensitivity of a mascara containing 0.4% Hydroxyethyl-cellulose. 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 (RTL 1978).

A conditioning polish remover containing 0.7% Hydroxypropylcellulose and a moisturizer containing 0.25% Cellulose Gum 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 later; all readings were negative for the polish remover, and one weak response was seen with the moisturizer (RTL 1977, 1979).

These same two products, the polish remover and the moisturizer, were further evaluated for photosensitivity in Draize-Shelanski RlPTs 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 (RTL 1977, 1979).

An eye product containing 0.605% Carboxymethylcellulose 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 (CTFA 1974).

Ocular Irritation

Three artificial tear solutions, one containing Hydroxyethylcellulose and one containing Hydroxypropyl Methylcellulose, were tested for dispersion action using 10 subjects (Capella and Schaefer 1974). 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 Hydroxyethylcellulose gave higher values of fluorescein uptake by the stroma and anterior chamber than either of the other solutions. The Hydroxyethylcellulose solution was a 30% more effective system (of fluorescein). No signs of irritation were reported in this study.

An eye lotion containing 0.5% Cellulose Gum produced no irritation when used around the eye (Chin et al. 1980).

Ludwig et al. (1992) examined the relationship between precorneal retention of viscous eye drops, discomfort and tear fluid composition after instillation of various cellulosic solutions (Hydroxyethylcellulose - MW 250,000; Hydroxypropylcellulose - MW 95,000; and Hydroxypropyl Methylcellulose - MW 150,000) using slit lamp fluorophotometry. The solution acceptability was evaluated by volunteers by answering a standard questionnaire. Five adult volunteers participated in the study.

Table 7. Clinical irritation and sensitization (Elder 1986).

Concentration tested	Type of test	No. tested	Results/Comments
	Cellulose Gum		
100%	Patch test (unspecified)	200	No primary dermal irritation, did not appear to be a sensitizer
100%	SIPT	200	non-irritating and non-sensitizing
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.
3.0% in wrinkle-smoothing cream	SIPT	15	No significant irritancy between test and controls
3.0% in wrinkle-smoothing cream	RIPT	89	essentially non-irritating and non-sensitizing
1.6% in foundation	RIPT	87	non-sensitizing
1.1% in product (not specified)	SIPT	19	All = 0.08; significantly milder than competitive control with All = 0.65
1.1% in medicated lotion	RIPT	86	non-irritating and non-sensitizing
1.1% in medicated lotion	21-day Cumulative Irritancy Assay	Not specified	No significant difference between test and controls
1.0% in paste mask	SIPT	19	All = 0.08; significantly milder than competitive control with All = 0.65
1.0% in paste mask	RIPT	97	non-irritating and non-sensitizing
0.5% in eyeliner	21-day Cumulative Irritancy Assay	17	essentially non-irritating
0.5% in eyeliner	RIPT	209	non-irritating and non-sensitizing
0.3% in moisturizing cream	21-day Cumulative Irritancy Assay	11	slightly irritating
0.3% in moisturizer	RIPT	210	non-irritating and non-sensitizing
0.25% in moisturizer	SIPT	105	non-irritating and non-sensitizing
0.25% in moisturizer	RIPT	49	non-irritating and non-sensitizing
0.25% in product (not specified)	Maximization test with SLS pre-treatment	25	non-irritating and non-sensitizing
0.2% in cleanser	210day Cumulative Irritancy Assay	17	essentially non-irritating
0.2% in cleanser	RIPT	209	Not a strong irritant and not a sensitizer
0.2% in makeup	RIPT	209	Not a strong irritant and not a sensitizer
0.2% in makeup	RIPT	206	non-sensitizing
0.605% in eye product	Maximization test with SLS pre-treatment	50	non-irritating, non-sensitizing
	Hydroxyethylcellulose		
100%	RIPT[a]	50	non-irritating, non-sensitizing
5%	RIPT	50	non-irritating, non-sensitizing
1% in hair cream rinse	RIPT with 5% aqueous dilution	54	non-irritating, non-sensitizing
0.75% in hair conditioner	RIPT with 50% aqueous dilution, challenge with 25% aqueous dilution	99	mildly irritating under occlusion, non-sensitizing
0.5% in hair conditioner	RIPT with 50% aqueous dilution, challenge with 25% aqueous dilution	99	mildly irritating, non-sensitizing

Table 7 (continued). Clinical irritation and sensitization (Elder 1986).

Concentration tested	Type of test	No. tested	Results/Comments
	Hydroxyethylcellulose (continued)		
0.5% in detangling rinse	RIPT with 10% aqueous solution	97	non-irritating, non-sensitizing
0.5% in mascara	21-day Cumulative Irritancy Assay	15	essentially non-irritating
0.5% in mascara	Maximization test with SLS[b] pre-treatment	15	essentially non-irritating
0.5% in mascara	Maximization test with SLS pre-treatment	25	non-sensitizing
0.5% 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
0.4% in mascara	21-day Cumulative Irritancy Assay	10	Total composite score of 32.73 (max=630); essentially non-irritating
0.4% in mascara	RIPT	107	non-sensitizing
0.3% in moisturizing cream	21-day Cumulative Irritancy Assay	12	essentially non-irritating
0.3% in moisturizing lotion	Anti-irritation test	10	HEC showed some anti-irritancy effects attributed to blocking of skin-reactive sites
2% in aqueous solution	RIPT	50	non-irritating, non-sensitizing
	Hydroxypropylcellulose		
10% in aqueous solution	SIPT[c]	7	Slight erythema seen in 3 subjects, slight to distinct dryness in 5 subjects
0.8% in antiperspirant	RIPT	97	non-irritating and non-sensitizing
0.8% in antiperspirant	RIPT	91	non-irritating and non-sensitizing
0.8% in body cleanser	RIPT	101	non-irritating and non-sensitizing
0.7% in conditioning polish remover	RIPT	51	essentially non-irritating and non-sensitizing
0.7% in conditioning polish remover	21-day Cumulative Irritancy Assay	27	essentially non-irritating
	Hydroxypropyl Methycellulose		
1.1% in facial cleanser	Controlled Use Study, 2 weeks	25	No signs of sensitization
	Methylcellulose		
100%	Patch test (unspecified)	200	No signs of irritation
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
0.25% in shampoo	RIPT tested as 10% dilution	50	Capable of inducing irritation, but non-sensitizing

Toxic Shock Syndrome

Hydroxyethylcellulose, Hydroxypropylcellulose, Methylcellulose, Cellulose Gum, and Carboxymethylcellulose all are used in tampons. Methylcellulose and Carboxymethylcellulose have been implicated in the development of Toxic Shock Syndrome (TSS) (Oram and Beck 1981). Tierno et al. (1983) have suggested that the Carboxymethylcellulose 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.

Mucosal Tissue Damage

Less adverse effects were produced by a suppository base composed of Hydroxypropylcellulose 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 Hydroxypropylcellulose 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 (Masuda et al. 1981).

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 Cellulose Gum (per subject) (Informatics 1972).

Laxative Effects

The World Health Organization (1974) has established an acceptable daily intake for man of up to 25 mg/kg body weight for Hydroxypropylcellulose, Hydroxypropylmethylcellulose, Methylcellulose, and Cellulose Gum; this intake level represents the sum total of modified celluloses.

Single oral doses of Methylcellulose ranging from 0.6 to 8.9 g have produced only mild laxative or constipating effects in man. Daily doses of 1-6 g Methylcellulose (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 Methylcellulose were effective as a laxative (Informatics 1972).

Similarly, Cellulose Gum 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 Cellulose Gum produced no serious side effects in 128 subjects. Daily doses of approximately 10 g Cellulose Gum for 6 months produced no hematological or toxic effects or mucosal irritation in 22 adults. Cellulose Gum 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 (Informatics 1972; FASEB 1974).

Inhalation Exposure

No inhalation studies have been reported, however, Clayton and Clayton (1981) state that long-term exposure to the dust of cellulose ethers in manufacturing operations has not led to any known adverse effects.

Dental Caries

Aithal et al. (1996) studied the clinical efficacy of Ethylcellulose and Methylcellulose as matrix materials used to control the release of F-1 from chewable tablets. These ingredients were evaluated for their effect on decay, missing, filled teeth (DMFT) and decay, missing, filled surfaces (DMFS). The ingredients of the 300 mg matrix tablets were sodium fluoride (2.0 mg), starch powder (15.0 mg), lactose (253.0 mg), and matrix materials (30.0 mg).

Seventy male and female school children (mean age 9 ± 1) years were the study subjects. The children all possessed similar eating habits and used water of fluoride content containing less than 0.3 ppm. They were divided into 2 groups (35 per group). The first group was treated with Methylcellulose matrix tablet and the second group received the Ethylcellulose matrix tablet containing sodium fluoride. The subjects were required to chew the tablets for 20 minutes and swish the saliva to come in contact with all the teeth. They were also advised not to swallow the tablet or the saliva, but to spit out the saliva only after the 20 minutes. At the completion of the 18 months, 52 children (28 in the Methylcellulose-treated group and 24 in the Ethylcellulose-treated group) remained for the clinical investigation.

The tablets were administered to the children 2 hours after lunch to both groups once a month for 18 months. The status of the dental caries was recorded surface wise and toothwise before and after the therapy. A detailed surface analysis was performed to see the cariostatic effect of fluoride from the controlled release tablets. The DMFT values before and after the treatment and the percentage difference with respect to the pre-treatment value was evaluated separately for permanent and temporary teeth.

The variation in the weight of the tablets, as well as the variation in the drug content in an average weight of a tablet were within the limits of ± 10. The moisture absorption was more for tablets containing Methylcellulose (1.25%) compared to those containing Ethylcellulose (0.49%). Eight percent of the drug was dissolved within 20 minutes. The hardness was maintained within 1.9 to 2.5 kg/cm^2 to facilitate the release of the drug within 20 minutes. The in vivo study revealed a decrease in the DMFT and DMFS values, which were indicative of a successful fluoride treatment for both primary and permanent teeth. There was a statistically significant decrease in the DMFT and DMFS values in permanent teeth for tablets containing Ethylcellulose compared to those containing Methylcellulose.

The authors concluded that the observations indicated that the fluoride therapy in the form of chewable tablets have a greater benefit on primary teeth as opposed to permanent teeth. The authors mentioned that this may be due to the newly erupted permanent teeth during the 18-month study, which did not undergo the same duration. The better efficacy of sodium fluoride chewable tablets containing Ethylcellulose as matrix materials on both permanent and primary teeth over those containing Methylcellulose may be due to the slow release of the active principle from the tablets, according to the authors. This 18-month clinical trial revealed the superiority of the Ethylcellulose matrix tablets over Methylcellulose matrix tablets in controlling the caries (Aithal et al. 1996).

Drug Delivery

Table 8 summarizes the numerous drugs/vaccines in which cellulose derivatives are used in drug delivery.

Shukla and Price (1991) studied the effect of drug loading and molecular weight of Cellulose Acetate Propionate on the release characteristics of theophylline microspheres. Microspheres with 40, 50, and 60% drug loading of anhydrous theophylline core material were prepared by the emulsion-solvent evaporation method. Three different molecular weights of Cellulose Acetate Propionate were used as encapsulating polymers. The geometric mean diameter of the microspheres increased with drug loading for all polymers. Dissolution rate for a given particle size fraction also increased with drug loading for all polymers. Higuchi/Baker-Lonsdale spherical matrix dissolution kinetics were followed by narrow particle size fractions of the microspheres. A linear relationship between the T-50% (time required for 50% of the drug to be released) and the square of microsphere diameter was observed with all three molecular weights of the encapsulants. The slowest drug release was obtained with the high molecular weight polymer, which also produced the smoothest microspheres.

Table 8. Drugs, vaccines, and medical devices for which cellulose derivatives are used, primarily as delivery vehicles.

Drug/Vaccine	Treatment (if mentioned)	Cellulose Derivative [a]	Reference
Theophylline monohydrate	Colon	EC, HEC, MCC	Alvarez-Fuentes et al. (2004)
Triclosan	*Streptococcus mutans* Biofilm	EC	Steinberg et al. (2006)
Chloropheniramine maleate	-	EC, HPMC	Tang et al. (1999)
Verapamil hydrochloride	-	EC, HPMC	El-Gazayerly et al. (2004)
Chlorpheniramine maleate	-	HPMC	Tang et al. (2000)
Verapamil hydrochloride	-	EC, HPMC	Lecomte et al. (2005)
Cisplatin	-	EC	Houjou et al. (1996)
Cisplatin	-	EC	Nakano et al. (1997)
Tamsulosin hydrochloride	-	EC	Kim et al. (2005)
Recombinant Human Granulocyte Colony-stimulating Factor (rhG-CSF)	-	EC	Takaya et al. (1995)
Piretanide	-	EC, HPC	Tsujiyama et al. (1990)
Piretanide	-	HPC, EC	Uekama et al. (1990)
Bermoprofen	Anti-inflammatory	EC, HPMC	Mori et al. (1991)
5-aminosalicylic acid	-	EC	Hu et al. (1999)
Theophylline	-	EC	Moldenhauer and Nairn (1990)
Propanol hydrochloride	-	EC, HPMC	Hutchings and Sakr (1994)
Diltiazem hydrochloride	-	EC	Murata and Noda (1994)
Alkannin	-	EC	Assimopoulou et al. (2003)
Shikonin	-	EC	Assimopoulou et al. (2003)
Aspirin	-	EC	Saravanan et al. (2003)
Diclofenac Diethylammonium Salt	-	EC	Arora and Mukherjee (2002)
Ketoprofen	-	EC, CMEC	Kamada et al. (2002)
Amoxicillin	Antibiotic	EC	Liu et al. (2005)
Propanolol hydrochloride	-	EC	Ubrich et al. (2004)
Chitosan	-	EC	Remunan-Lopez et al. (1998)
Ibuprofen	-	C, HPMC	Majid Khan and Zhu (1998)
Propanolol hydrochloride	-	HPMC, EC	Mehuys et al. (2005)
Buflomedil hydrochloride	-	C, EC	Sungthongjeen et al. (2004)
Phenobarbitol	-	EC	Lee and Lee (1989)
Diphenhydramine hydrochloride	-	EC	Huang and Ghebre-Sellassie (1989)
Zinc sulfate	-	EC	Oner et al. (1988)
Nifedipine	-	EC	Mallick et al. (2000)
Diclofenac sodium	-	EC	Guo et al. (2003)
Diltiazem hydrochloride	-	HPMC, EC	Zhang and Zhu (2002)
Metronidazole	-	EC	Huang and Lu (2002)
Diltiazem hydrochloride	-	EC	Fan et al. (2002)
Ampicillin	-	EC	Chen et al. (2005)

Table 8 (continued). Drugs, vaccines, and medical devices for which cellulose derivatives are used, primarily as delivery vehicles.

Drug/Vaccine	Treatment (if mentioned)	Cellulose Derivative [a]	Reference
Alcohol	Venous malformation	EC	Dompmartin et al. (2000)
Cisplatin	-	EC	Wang (1991)
Rifampicin	-	EC	Sreenivasa Rao et al. (2001)
Xanthine derivatives	-	EC	Neau et al. (1999)
Benzoyl peroxide	-	EC	Jelvehgari et al. (2006)
Diclofenac sodium	-	EC	Al-Omran et al. (2002)
Diltiazem hydrochloride	-	EC	Bhalerao et al. (2001)
Actinobacillus pleuropneumoniae antigens	-	EC	Liao et al. (2001)
Aspirin	-	EC	Yang et al. (2001)
Propanolol hydrochloride	-	EC	Elkharraz et al. (2003)
Cellulose triacetate (CTA) and poly (α-methyl styrene) (PMS)	-	EC	Tsai et al. (2000)
Tolnaftate	-	EC	Dash et al. (2002)
Zidovudine (AZT)	-	EC	Abu-Izza et al. (1996)
Verapamil hydrochloride	-	EC, HPMC	Streubel et al. (2000)
Diltiazem hydrochloride, Verapamil, and Sodium carboxymethylstarch	-	EC	Fan et al. (2001)
Caffeine (model drug)	Colon	EC	Muraoka et al. (1998)
Ketoprofen	-	EC, CMEC	Yamada et al. (2001)
Prednisolone	-	EC	Di Colo et al. (2006)
Theophylline	-	HPC, EC	Dashevsky and Mohamad (2006)
Didanosine	Acquired immuno deficiency syndrome (AIDS)	EC	Sanchez-LaFuente et al. (2002)
Naproxen	-	EC, MC	Duarte et al. (2006)
Loratidine	-	EC	Martinac et al. (2005)
Propanolol hydrochloride	-	EC	Pearnchob and Bodmeier (2003)
Nifedipine	-	EC	Huang et al. (2006)
Metoclopramide	-	EC	Sadeghi et al. (2003)
Potassium chloride	-	EC	Wu et al. (2003)
Polyvinyl acohol	-	EC, HPMC	Morita et al. (2000)
Diclofenac sodium	-	EC	Lin et al. (2001)
Theophylline	-	HPMC	Hayashi et al. (2005)
5-Aminosalicylic acid	Crohn's disease	EC	Tromm et al. (1999)
Theophylline	-	EC	Ikegami et al. (2006)
Indomethacin (IND)	-	EC, HPMC	Ohara et al. (2005)
Diltiazem	-	EC, HPMC	Miyazaki et al. (2000)
Pentoxifylline	-	MHEC, HPMC	Freichel and Lippold (2001)
Hydroxyurea	Nasal	HEC	Dayal et al. (2005)
Fluoride	Enamel remineralization	HEC	Arnold et al. (2006)

Table 8 (continued). Drugs, vaccines, and medical devices for which cellulose derivatives are used, primarily as delivery vehicles.

Drug/Vaccine	Treatment (if mentioned)	Cellulose Derivative [a]	Reference
Pulsincap™	Colon	EC	Niwa et al. (1995)
Vancomycin	-	HEC	Giandalia et al. (2001)
Sodium dodecylsulfate	-	C	Rodriguez et al. (2003)
Vancomycin	-	HEC	Bartolotta et al. (2005)
Theophylline	-	HEC, HPMC	Uner and Altinkurt (2004)
Cidofovir	-	HEC	Cundy et al. (1997)
Formulin	-	HEC	Hashimoto et al. (2001)
Human Leukocyte Interferon-α	Intravaginal warts	HEC	Syed and Ahmadpour (1998)
Acetic acid	-	HEC	Coufal et al. (2003)
Chloropheniramine maleate	-	HPC, HEC	Sinha and Rohera (2002)
Pentoxifylline and Vancomycin hydrochloride	-	HEC, HPMC. HPC	Sasa et al. (2006)
Flurbiprofen	Gingivitis	HEC	Jones et al. (1999)
Heparin	-	HEC	Schmitz et al. (2005)
Metronidazole	Periodontal disease	HEC	Perioli et al. (2004)
Diclofenac	-	HEC	Azechi et al. (2000)
Piroxicam	Anti-inflammatory	HEC	Canto et al. (1999)
Metronidazole	-	M, HEC	Varshosaz et al. (2002)
Acetominophen	-	HEC	Guo et al. (1999)
Trehalose	-	HEC	Matsuo (2001)
Cefpodoxime	-	HPMC	Merchant et al. (2006)
Verapamil hydrochloride	-	HPMC	Chen et al. (2006)
Piroxicam	-	HPMC, HPC, HEC	Attia et al. (2004)
Erythromycin	Acne	HEC	Vermeulen et al. (1999)
Flurbiprofen	-	EC	Mallick et al. (2002)
Ibuprofen	-	HPMC	Ridell et al. (1999)
Soybean isoflavones (hormonal)	-	EC, HPC	Setchell et al. (2005)
Alachlor (herbicide)	-	EC	Fernandez - Urrusuno et al. (2000)
Norflurazon (herbicide)	-	EC	Sopena et al. (2005)
Plant extracts	Antimicrobial	EC	Meunier et al. (2006)
Maxillary arterial embolization	Medical device use	EC	Yang et al. (1995)

[a] EC = Ethylcellulose; HEC = Hydroxyethylcellulose; MCC = Methylcarboxycellulose; HPMC - Hydroxypropylmethylcellulose; C = Cellulose; HPC - Hydroxypropylcellulose; MHEC = Methylhydroxyethylcellulose.

Baeyens et al. (1998) evaluated the soluble bioadhesive ophthalmic drug inserts (BODI) for prolonged release of gentamicin sulfate (GS) in tears. The BODI's (length 5.0 mm, diameter 2.0 mm, weight 20.5 mg, average GS content 5.0 mg) were prepared by extrusion of a mixture based on Hydroxypropylcellulose (HPC), Ethylcellulose (EC), and carbomer. Two methods were tested to prolong the release of GS in tears: (1) preliminary treatment of GS and (2) use of a less hydrophilic polymer than HPC, Hydroxypropyl Methylcellulose, as a vehicle constituent. The preliminary treatment consisted of the formation of a GS/cellulose acetate phthalate (CAP) solid dispersion (ratio GS/CAP: 10/6) made in acetonic medium, and

in the coating of GS/EC granules (GS/EC ratio: 10/0.5) with an aqueous dispersion of CAP, to form a GS/EC/CAP coprecipitate (GS/EC/CAP ratio: 10/0.5/6).

Ophthalmic inserts containing GS/CAP solid dispersion, GS/EC/CAP coprecipitate and Hydroxypropyl Methylcellulose resulted in improved time of efficiency (t_{eff}) (43.8, 23.3, and 33.1 h, respectively), when compared to inserts containing GS without preliminary treatment (t_{eff} = 11.9 h). A high irritation level was observed for inserts containing GS containing the GS/EC/CAP and Hydroxypropyl Methylcellulose. A relation between t_{eff} and irritation score was established, emphasizing the importance of irritability as a factor during the evaluation of the potential of these systems (Baeyens et al. 1998).

SUMMARY

The Cosmetic Ingredient Review (CIR) Expert Panel evaluated in 1986 the safety of Hydroxyethylcellulose, Hydroxypropylcellulose, Methylcellulose, Hydroxypropyl Methylcellulose, and Cellulose Gum in cosmetics, concluding that these ingredients are "safe as cosmetic ingredients in the present practices of use and concentration". The CIR Expert Panel has further considered other related ingredients and determined that the available data support the safety of cellulose and a larger group of modified cellulose polymers. Accordingly, this report has been modified to include other ingredients: Calcium Carboxymethyl Cellulose, Carboxymethyl Cellulose Acetate Butyrate, Carboxymethyl Hydroxyethylcellulose, Cellulose, Cellulose Acetate, Cellulose Acetate Butyrate, Cellulose Gum, Cellulose Acetate Propionate, Cellulose Acetate Propionate Carboxylate, Cellulose Succinate, Cetyl Hydroxyethylcellulose, Ethylcellulose, Hydrolyzed Cellulose Gum, Hydroxybutyl Methylcellulose, Hydroxyethylcellulose, Hydroxyethyl Ethylcellulose, Hydroxypropylcellulose, Hydroxypropyl Methylcellulose, Hydroxypropyl Methylcellulose Acetate/Succinate, Methylcellulose, Methyl Ethylcellulose, Methyl Hydroxyethylcellulose, Microcrystalline Cellulose, Potassium Cellulose Succinate, and Sodium Cellulose Sulfate.

Hydroxyethylcellulose, Hydroxypropylcellulose, Methylcellulose, Hydroxypropylmethylcellulose, and Cellulose Gum 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 polymers 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 88%; however, the celluloses are most frequently used in concentrations of >0.1-1%.

The cellulose derivatives are used widely as an ingredient in pharmaceutical and industrial products. Cellulose Gum, Cellulose Acetate, Ethylcellulose, and Methylcellulose 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 Cellulose Gum, 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 Hydroxypropylcellulose in mice and rats and Carboxymethylcellulose in dogs were nontoxic; however, iv injections of Methylcellulose to dogs and rabbits produced hematological reactions, retention and accumulation of Methylcellulose 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% Cellulose Gum.

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 Cellulose Gum were nontoxic in rats.

Subchronic iv administration of up to 10.0% Hydroxyethylcellulose 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 Hydroxyethylcellulose storage by the presence of swollen hepatic, glomerular endothelial, and endocardial cells. Similar effects were noted in dogs given repeated iv injections of Methylcellulose and Carboxymethylcellulose.

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.

Hydroxypropylmethylcellulose was nonsensitizing in guinea pigs at concentrations up to 25%, whereas cosmetic products containing Hydroxyethylcellulose and Cellulose Gum were nonphototoxic in rabbits.

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

Methylcellulose, Carboxymethylcellulose, and Cellulose Gum were nonmutagenic in various tests both with and without metabolic activation. Methylcellulose was also nontumorigenic when injected subcutaneously in black rats. When injected ip, Methylcellulose 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 Hydroxypropylcellulose, Hydroxypropylmethylcellulose, Methylcellulose, and Cellulose Gum; this intake level represents the sum total of modified celluloses. Daily doses of up to 6 g Methylcellulose 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 Cellulose Gum 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% Cellulose Gum.

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 Methylcellulose and Carboxymethylcellulose in tampons has been implicated in the development of Toxic Shock Syndrome. Carboxymethylcellulose 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 Cellulose Gum 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.

DISCUSSION

The CIR Expert Panel noted that the ingredients in the original safety assessment are modified cellulose polymers derived from the reaction of 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 substitute group, largely determine the physical properties, particularly solubility, of the product. So, also, are the properties of other modified cellulose polymers, e.g., Hydroxybutyl Methylcellulose, which differs very little from Hydroxypropyl Methylcellulose in the original safety assessment.

In the absence of inhalation toxicity data, the Panel determined that these modified Cellulose polymers can be used safely in hair sprays, because the ingredient particle size is not respirable. The Panel reasoned that the particle size of aerosol hair sprays (~38 μm) and pump hair sprays (>80 μm) is large compared to respirable particulate sizes (≤10 μm).

The cellulose derivatives pass essentially unchanged through the gastrointestinal tract following oral administration to rats, dogs, and man. The Expert Panel noted that acute, subchronic, chronic toxicity, reproductive and developmental toxicity, genotoxicity, and carcinogenicity studies of cellulose derivatives indicate that they are practically non-toxic when administered by oral, intraperitoneal, subcutaneous, or dermal routes. While no clinical inhalation studies have been conducted, long-term exposure to the dust of cellulose ethers in manufacturing operations has not led to any significant adverse effects. Ocular and dermal irritation studies indicate that the cellulose derivatives are, at most, minimally irritating and are not dermal sensitizers. Clinical studies confirm these findings.

The CIR Expert Panel recognizes that there are data gaps regarding use and concentration of some of these ingredients. However, the overall information available on the types of products in which these ingredients are used and at what concentrations indicate a pattern of use, which was considered by the Expert Panel in assessing safety.

AMENDED CONCLUSION

On the basis of the data presented in this report, the CIR Expert Panel concludes that Cellulose, Calcium Carboxymethylcellulose, Carboxymethyl Cellulose Acetate Butyrate, Carboxymethyl Hydroxyethylcellulose, Cellulose Acetate, Cellulose Acetate Butyrate, Cellulose Acetate Propionate Carboxylate, Cellulose Gum, Cellulose Acetate Propionate, Cellulose Succinate, Cetyl Hydroxyethylcellulose, Ethylcellulose, Hydrolyzed Cellulose Gum, Hydroxybutyl Methylcellulose, Hydroxyethylcellulose, Hydroxyethyl Ethylcellulose, Hydroxypropylcellulose, Hydroxypropyl Methylcellulose, Hydroxypropyl Methylcellulose Acetate/Succinate, Methylcellulose, Methyl Ethylcellulose, Methyl Hydroxyethylcellulose, Microcrystalline Cellulose, Potassium Cellulose Succinate, and Sodium Cellulose Sulfate are safe as cosmetic ingredients in the practices of use and concentration given in this safety assessment.[1]

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[1] Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in the group.

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SAFETY DATA SHEET

Version 6.1
Revision Date 01/15/2020
Print Date 02/08/2020

SECTION 1: Identification of the substance/mixture and of the company/undertaking

1.1 Product identifiers

Product name : Cellulose acetate

Product Number : 180955
Brand : Aldrich
CAS-No. : 9004-35-7

1.2 Relevant identified uses of the substance or mixture and uses advised against

Identified uses : Laboratory chemicals, Synthesis of substances

1.3 Details of the supplier of the safety data sheet

Company : Sigma-Aldrich Inc.
3050 Spruce Street
ST. LOUIS MO 63103
UNITED STATES

Telephone : +1 314 771-5765
Fax : +1 800 325-5052

1.4 Emergency telephone number

Emergency Phone # : +1-703-527-3887

SECTION 2: Hazards identification

2.1 Classification of the substance or mixture

Not a hazardous substance or mixture.

2.2 GHS Label elements, including precautionary statements

Not a hazardous substance or mixture.

2.3 Hazards not otherwise classified (HNOC) or not covered by GHS - none

SECTION 3: Composition/information on ingredients

3.1 Substances

Synonyms : Acetylcellulose

CAS-No. : 9004-35-7

No components need to be disclosed according to the applicable regulations.

SECTION 4: First aid measures

4.1 Description of first aid measures

If inhaled
If breathed in, move person into fresh air. If not breathing, give artificial respiration.

In case of skin contact
Wash off with soap and plenty of water.

In case of eye contact
Flush eyes with water as a precaution.

If swallowed
Never give anything by mouth to an unconscious person. Rinse mouth with water.

4.2 Most important symptoms and effects, both acute and delayed

The most important known symptoms and effects are described in the labelling (see section 2.2) and/or in section 11

4.3 Indication of any immediate medical attention and special treatment needed

No data available

SECTION 5: Firefighting measures

5.1 Extinguishing media

Suitable extinguishing media
Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.

5.2 Special hazards arising from the substance or mixture

Carbon oxides

5.3 Advice for firefighters

Wear self-contained breathing apparatus for firefighting if necessary.

5.4 Further information

No data available

SECTION 6: Accidental release measures

6.1 Personal precautions, protective equipment and emergency procedures

Avoid dust formation. Avoid breathing vapours, mist or gas.
For personal protection see section 8.

6.2 Environmental precautions

No special environmental precautions required.

6.3 Methods and materials for containment and cleaning up

Sweep up and shovel. Keep in suitable, closed containers for disposal.

6.4 Reference to other sections

For disposal see section 13.

SECTION 7: Handling and storage

7.1 Precautions for safe handling

Further processing of solid materials may result in the formation of combustible dusts. The potential for combustible dust formation should be taken into consideration before additional processing occurs.
Provide appropriate exhaust ventilation at places where dust is formed.
For precautions see section 2.2.

7.2 Conditions for safe storage, including any incompatibilities

Keep container tightly closed in a dry and well-ventilated place.
Storage class (TRGS 510): 13: Non Combustible Solids

7.3 Specific end use(s)

Apart from the uses mentioned in section 1.2 no other specific uses are stipulated

SECTION 8: Exposure controls/personal protection

8.1 Control parameters

Components with workplace control parameters
Contains no substances with occupational exposure limit values.

8.2 Exposure controls

Appropriate engineering controls
General industrial hygiene practice.

Personal protective equipment

Eye/face protection
Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU).

Skin protection
Handle with gloves. Gloves must be inspected prior to use. Use proper glove removal technique (without touching glove's outer surface) to avoid skin contact with this product. Dispose of contaminated gloves after use in accordance with applicable laws and good laboratory practices. Wash and dry hands.

Full contact
Material: Nitrile rubber
Minimum layer thickness: 0.11 mm
Break through time: 480 min
Material tested:Dermatril® (KCL 740 / Aldrich Z677272, Size M)

Splash contact
Material: Nitrile rubber
Minimum layer thickness: 0.11 mm
Break through time: 480 min
Material tested:Dermatril® (KCL 740 / Aldrich Z677272, Size M)

data source: KCL GmbH, D-36124 Eichenzell, phone +49 (0)6659 87300, e-mail sales@kcl.de, test method: EN374
If used in solution, or mixed with other substances, and under conditions which differ from EN 374, contact the supplier of the CE approved gloves. This recommendation is advisory only and must be evaluated by an industrial hygienist and safety officer familiar with the specific situation of anticipated use by our

customers. It should not be construed as offering an approval for any specific use scenario.

Body Protection
Choose body protection in relation to its type, to the concentration and amount of dangerous substances, and to the specific work-place., The type of protective equipment must be selected according to the concentration and amount of the dangerous substance at the specific workplace.

Respiratory protection
Respiratory protection is not required. Where protection from nuisance levels of dusts are desired, use type N95 (US) or type P1 (EN 143) dust masks. Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU).

Control of environmental exposure
No special environmental precautions required.

SECTION 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties

a)	Appearance	Form: solid
b)	Odour	No data available
c)	Odour Threshold	No data available
d)	pH	No data available
e)	Melting point/freezing point	No data available
f)	Initial boiling point and boiling range	No data available
g)	Flash point	()No data available
h)	Evaporation rate	No data available
i)	Flammability (solid, gas)	No data available
j)	Upper/lower flammability or explosive limits	No data available
k)	Vapour pressure	No data available
l)	Vapour density	No data available
m)	Relative density	1.3 g/mL at 25 °C (77 °F)
n)	Water solubility	No data available
o)	Partition coefficient: n-octanol/water	No data available
p)	Auto-ignition temperature	No data available
q)	Decomposition temperature	No data available
r)	Viscosity	No data available

s) Explosive properties No data available

t) Oxidizing properties No data available

9.2 Other safety information
No data available

SECTION 10: Stability and reactivity

10.1 Reactivity
No data available

10.2 Chemical stability
Stable under recommended storage conditions.

10.3 Possibility of hazardous reactions
No data available

10.4 Conditions to avoid
No data available

10.5 Incompatible materials
Strong oxidizing agents

10.6 Hazardous decomposition products
Hazardous decomposition products formed under fire conditions. - Carbon oxides
Other decomposition products - No data available
In the event of fire: see section 5

SECTION 11: Toxicological information

11.1 Information on toxicological effects

Acute toxicity
LD50 Oral - Rat - > 5,050 mg/kg
Inhalation: No data available
Dermal: No data available
No data available

Skin corrosion/irritation
No data available

Serious eye damage/eye irritation
No data available

Respiratory or skin sensitisation
No data available

Germ cell mutagenicity
No data available

Carcinogenicity

IARC: No component of this product present at levels greater than or equal to 0.1% is identified as probable, possible or confirmed human carcinogen by IARC.

ACGIH: No component of this product present at levels greater than or equal to 0.1% is identified as a carcinogen or potential carcinogen by ACGIH.

NTP: No component of this product present at levels greater than or equal to 0.1% is identified as a known or anticipated carcinogen by NTP.

OSHA: No component of this product present at levels greater than or equal to 0.1% is on OSHA's list of regulated carcinogens.

Reproductive toxicity
No data available
No data available

Specific target organ toxicity - single exposure
No data available

Specific target organ toxicity - repeated exposure
No data available

Aspiration hazard
No data available

Additional Information
RTECS: Not available

To the best of our knowledge, the chemical, physical, and toxicological properties have not been thoroughly investigated.

SECTION 12: Ecological information

12.1 Toxicity
No data available

12.2 Persistence and degradability
No data available

12.3 Bioaccumulative potential
No data available

12.4 Mobility in soil
No data available

12.5 Results of PBT and vPvB assessment
PBT/vPvB assessment not available as chemical safety assessment not required/not conducted

12.6 Other adverse effects
No data available

SECTION 13: Disposal considerations

13.1 Waste treatment methods

Product
Offer surplus and non-recyclable solutions to a licensed disposal company.

Contaminated packaging
Dispose of as unused product.

SECTION 14: Transport information

DOT (US)
Not dangerous goods

IMDG
Not dangerous goods

IATA
Not dangerous goods

SECTION 15: Regulatory information

SARA 302 Components
No chemicals in this material are subject to the reporting requirements of SARA Title III, Section 302.

SARA 313 Components
This material does not contain any chemical components with known CAS numbers that exceed the threshold (De Minimis) reporting levels established by SARA Title III, Section 313.

Massachusetts Right To Know Components
No components are subject to the Massachusetts Right to Know Act.

Pennsylvania Right To Know Components

Cellulose acetate	CAS-No. 9004-35-7	Revision Date

New Jersey Right To Know Components

Cellulose acetate	CAS-No. 9004-35-7	Revision Date

California Prop. 65 Components
This product does not contain any chemicals known to State of California to cause cancer, birth defects, or any other reproductive harm.

SECTION 16: Other information

Further information

The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Corporation and its Affiliates shall not be held liable for any damage resulting from handling or from contact with the above product. See www.sigma-aldrich.com and/or the reverse side of invoice or packing slip for additional terms and conditions of sale.

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