Toxicological profile for

Hydroxypropylcellulose

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

2-Hydroxypropyl 2,3,6-tris-O-(2-hydroxypropyl)-4-O-[2,3,4,6-tetrakis-O-(2-hydroxypropyl)-α-D-glucopyranosyl]-β-D-glucopyranoside (ChemSpider)

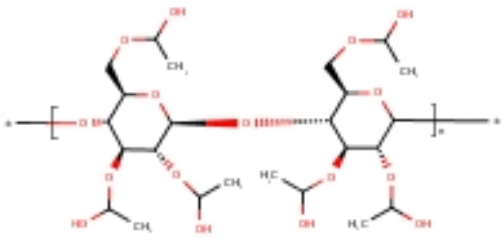
1.2. Synonyms

2,3,6-Tris-O-(2-hydroxypropyl)-b-D-glucopyranose; 2-Hydroxypropyl cellulose; Cellulose 2-hydroxypropyl ether; Cellulose hydroxypropyl ether; Cellulose, 2- hydroxypropyl ether; Cellulose, 2-hydroxypropyl ester; Hydroxypropyl cellulose; Cellulose, 2-hydroxypropyl ether; Celulosa, 2-hidroxipropil ter; E 463; E463; HPC-L; HYDROXYPROPYL CELLULOSE (650000 WAMW); Hydroxypropyl; Hydroxypropyl cellulose; Hydroxypropyl cellulose [INN:NF]; Hydroxypropyl ether of cellulose; Hydroxypropylcellulose; Hydroxypropylcellulose of Low-substitution; Hydroxypropylcellulose of low substitution; Hyprolose [INN]; Hyprolosum; Klucel; LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (11% HYDROXYPROPYL; 100000 MW); LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (11% HYDROXYPROPYL; 130000 MW); Lacrisert; Low-substituted hydroxypropyl cellulose (L-HPC) (ToxInfo)

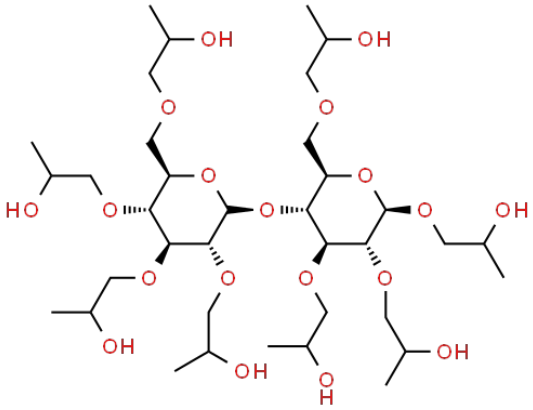
1.3. Molecular formula

C3-H8-O2.x-Unspecified (ToxInfo); C36H70O19 (ChemSpider).

1.4. Structural Formula



(ChemSpider)



1.5. Molecular weight (g/mol)

354.39 (ToxInfo); 806.930 (ChemSpider)

1.6. CAS registration number

9004-64-2

1.7. Properties

1.7.1. Melting point

>130°C (IGS, 2021)

1.7.2. Boiling point

891.2±65.0°C at 760 mmHg (estimated) (ChemSpider)

1.7.3. Solubility

soluble up to 40°C; insoluble > 40°C (CIR 2009)

1.7.4. pKa

No data available to us at this time.

1.7.5. Flashpoint

492.8±34.3°C (estimated) (ChemSpider)

1.7.6. Flammability limits (vol/vol%)

No data available to us at this time.

1.7.7. (Auto)ignition temperature

No data available to us at this time.

1.7.8. Decomposition temperature

No data available to us at this time.

1.7.9. Stability

No data available to us at this time.

1.7.10. Vapor pressure

0.0±0.6 mmHg at 25°C (estimated) (ChemSpider)

1.7.11. log Kow

-1.24 (estimated) (ChemSpider)

2. General information

2.1. Exposure

Hydroxypropylcellulose has a function of binder, emulsion stabilizers, film former, viscosity increasing agent in cosmetic (CIR 2009).

Current uses (FDA 2009) of Hydroxypropylcellulose reported in the Voluntary Cosmetic Registration Program (VCRP) total 97, with the largest uses in “other” shaving preparations. No current use concentrations were reported in an industry survey (Council 2009). (CIR 2009)

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 emulsifier, 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). (CIR 2009)

Hydroxypropylcellulose (CAS RN 9004-64-2) is used as a binding, surfactant - emulsifying, emulsion stabilising, film forming and viscosity controlling ingredient in cosmetics in the EU.

As taken from CosIng (Cosmetic substances and ingredients database).

Hydroxypropyl cellulose (CAS RN 9004-64-2) is listed as an ingredient in personal care and pet care products by the CPID.

“Dietary exposure to L-HPC [low-substituted hydroxypropyl cellulose] from its proposed use as a new food additive was estimated combining the food consumption data available within the EFSA Comprehensive European Food Consumption Database with the proposed use levels provided by the applicant. The Panel noted that the exposure data from the proposed use and use level of L-HPC was around 2 mg/kg body weight (bw) per day for high-level consumers at the highest use level. This value is very low in comparison with around 500 mg/kg bw per day for high-level consumers of other modified celluloses, which was not considered as a safety concern by the Panel in the re-evaluation of the celluloses”

Estimate exposure to low-hydroxypropyl cellulose (L-HPC) from its proposed use as a food additive: at the proposed use levels and at the proposed MLs

Estimate exposure (mg/kg bw per day	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
Proposed typical use level: 10,000 mg/kg				
Mean	0–0.26	0–0.095	0–0.25	0–0.54
High level	0–0.94	0–0.44	0–0.85	0–0.85
Estimate exposure (mg/kg bw per day	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
Proposed typical use level: 20,000 mg/kg				
Mean	0–0.52	0–0.19 0	0–0.5	0–1.08
High level	0–1.89	0–0.88	0–1.7	0–1.7

As taken from EFSA, 2018a.

The EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) considered an indicative total exposure of around 660–900 mg/kg bw per day for microcrystalline, powdered and modified celluloses.

As taken from EFSA, 2018b

“Used to make solutions of varying viscosity; Used as an emulsifier, stabilizer, whipping aid, film former, thickener, and protective in foods; Also used as a binder (ceramics and glazes), additive (hair and cosmetic products, blow-molded bottles, PVC polymerization, and pharmaceuticals), and therapeutic agent (topical protectant); [Merck Index] Used in contact lens wetting solutions; [ChemIDplus] Used as a formulation aid, emulsifier, stabilizer or thickener, and texturizer for foods; [FDA].”

As taken from Haz-Map, 2020

Hydroxypropylcellulose (CAS RN 9004-64-2) is used as a binder, coating agent, disintegrant, emulsifying agent, film former, gelling agent, lubricant, stabilizing agent, suspending agent - nonsurfactant, thickening agent and viscosity increasing agent in non-medicinal natural health products. It has an upper limit toxicity restriction of 30 mg/kg bw/day (Health Canada, 2021).

2.2. Combustion products

No data available to us at this time.

2.3. Ingredient(s) from which it originates

Plant or synthetic (CIR 2009).

“Pure cellulose (wood pulp) is subjected to partial etherification with propylene oxide. The resulting product is than purified, dried and milled to yield low-substituted hydroxypropyl cellulose” (EFSA, 2018a).

“Methyl cellulose (E 461), ethyl cellulose (E 462), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464) and ethyl methyl cellulose (E 465) are celluloses obtained synthetically from fibrous plant material. Each of the celluloses is partially etherified with methyl groups, ethyl groups, hydroxypropyl groups and contains a small degree of hydroxypropyl substitution, and methyl and ethyl groups, respectively” (EFSA, 2018b).

3. Status in legislation and other official guidance

The CEF Panel concluded that the substances: iron, sodium chloride, water, silica gel, activated carbon, monosodium glutamate, potassium acid tartrate, powdered cellulose, malic acid, chabazite, hydroxypropyl cellulose, potassium carbonate, sodium thiosulfate, propylene glycol, glycerin, polyethyleneglycol sorbitan monooleate, sodium propionate and clinoptilolite, do not raise a safety concern when used in oxygen absorbers in sachets, patches or cards, placed in the headspace of the packaging or when used in direct contact with food, excluding liquid food or foods that have an external aqueous liquid phase on the surface such as sliced fruits and fresh meat. (EFSA, 2013)

Hydroxypropyl cellulose is authorised as additive or monomer for plastic materials and articles in contact with foods (Regulation (EU) No 10/2011) with no specific restriction (FCM Substance No 559). (EFSA, 2013)

Estimate of acceptable daily intake for man mg/kg body weight:

Unconditional acceptance 0-30;

Conditional acceptance: Higher levels for dietetic and calory control purposes. (JECFA 1969).

Summary of Evaluations Performed by the Joint FAO/WHO Expert Committee on Food Additives: **ADI:** NOT SPECIFIED **Comments:** Group ADI for modified celluloses: ethyl cellulose, ethyl hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methylcellulose, methyl ethyl cellulose, and sodium carboxymethyl cellulose (JECFA 1989).

Included on the FDA’s Inventory of Inventory of Food Contact Substances Listed in 21 CFR and Substances Added to Food (formerly EAFUS) as an emulsifier or emulsifier salt, formulation aid, stabilizer or thickener, and texturizer, and is covered under 21 CFR 172.870, is a substance for Use as Basic Components of Single and Repeated Use Food Contact Surfaces (cellophane 21 CFR 177.1200) and is also covered under 21 CFR section 73.1001 (Diluents in color additive mixtures for drug use exempt from certification) (FDA, 2024a,b).

Hydroxypropyl cellulose (E463) is authorised for use as a food additive in the EU under legislation nos 1333/2008 and 1129/2011 and, as a Group I additive, also under nos 438/2013, 2015/0647, 2015/1832 and 2018/1497 (European Commission, a,b). Low-substituted hydroxypropyl cellulose (L-HPC) (E463a) is also authorised under legislation no. 2018/1461 (European Commissionc).

Cellulose, 2-hydroxypropyl ether (CAS RN 9004-64-2) is listed on the US EPA InertFinder Database as approved for food and non-food use pesticide products. Cellulose, 2-hydroxypropyl ether (CAS RN 9004-64-2) is not registered under REACH (ECHA)

Hydroxypropyl cellulose (CAS RN 9004-64-2) is not classified for packaging and labelling under Regulation (EC) No. 1272/2008 (ECHA, 2024).

Hydroxypropyl cellulose (CAS RN 9004-64-2) is included on the US EPA’s list of Safer Chemical Ingredients (US EPA, 2024).

Cellulose, 2-hydroxypropyl ether is included on the US EPA Toxic Substances Control Act (TSCA) inventory, 2024 CDR TSCA Inventory and on the US EPA 2024 CDR Full Exempt list (Chemical Data Reporting Rule).

The TSCA inventory and 2024 CDR Full Exempt list.

The EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) “concluded that there would be no safety concern at the proposed uses and use levels for L-HPC” (low-substituted hydroxypropyl cellulose) as a food additive in food supplements in solid form (tablet).

As taken from EFSA, 2018a.

The EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), in a re-evaluation of celluloses E 460(i), E 460(ii), E 461, E 462, E 463 (hydroxypropyl cellulose), E 464, E 465, E 466, E 468 and E 469 as food additives, “concluded that there was no need for a numerical ADI and that there would be no safety concern at the reported uses and use levels for the unmodified and modified celluloses (E 460(i); E 460(ii); E 461–466; E 468 and E 469).”

As taken from EFSA, 2018b

Cellulose, 2-hydroxypropyl ether (CAS RN 9004-64-2) has been identified as a chemical of “low concern to human health by application of expert validated rules under the NICNAS targeted tier I approach” and “poses no unreasonable risk to human health based on Tier I assessment under the NICNAS IMAP assessment framework” (AICIS, 2017).

Hydroxypropyl cellulose and low-substituted hydroxypropyl cellulose (both CAS RN 9004-64-2) 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 and maximum daily exposures:

Inactive Ingredient	**Route**	**Dosage Form**	**CAS Number**	**UNII**	**Maximum Potency per unit dose**	**Maximum Daily Exposure (MDE)**
HYDROXYPROPYL CELLULOSE	ORAL	GRANULE, FOR SUSPENSION	9004642	9XZ8H6N6OH		251mg
HYDROXYPROPYL CELLULOSE	ORAL	TABLET	9004642	9XZ8H6N6OH		128mg
HYDROXYPROPYL CELLULOSE	ORAL	TABLET, DELAYED RELEASE	9004642	9XZ8H6N6OH		4mg
HYDROXYPROPYL CELLULOSE	ORAL	TABLET, EXTENDED RELEASE	9004642	9XZ8H6N6OH		413mg
HYDROXYPROPYL CELLULOSE	ORAL	TABLET, FILM COATED	9004642	9XZ8H6N6OH		25mg
HYDROXYPROPYL CELLULOSE (110000 WAMW)	ORAL	CAPSULE	9004642	5Y0974F5PW		139mg
HYDROXYPROPYL CELLULOSE (110000 WAMW)	ORAL	CAPSULE, DELAYED RELEASE	9004642	5Y0974F5PW		90mg

HYDROXYPROPYL CELLULOSE (110000 WAMW)	ORAL	CAPSULE, EXTENDED RELEASE	900464 2	5Y0974F5PW		375mg
HYDROXYPROPYL CELLULOSE (110000 WAMW)	ORAL	GRANULE	900464 2	5Y0974F5PW		8mg
HYDROXYPROPYL CELLULOSE (110000 WAMW)	ORAL	SUSPENSION	900464 2	5Y0974F5PW		1249mg
HYDROXYPROPYL CELLULOSE (110000 WAMW)	ORAL	TABLET	900464 2	5Y0974F5PW		613mg
HYDROXYPROPYL CELLULOSE (110000 WAMW)	ORAL	TABLET, CHEWABLE	900464 2	5Y0974F5PW		1050mg
HYDROXYPROPYL CELLULOSE (110000 WAMW)	ORAL	TABLET, DELAYED RELEASE	900464 2	5Y0974F5PW		528mg
HYDROXYPROPYL CELLULOSE (110000 WAMW)	ORAL	TABLET, EXTENDED RELEASE	900464 2	5Y0974F5PW		356mg
HYDROXYPROPYL CELLULOSE (110000 WAMW)	ORAL	TABLET, FILM COATED	900464 2	5Y0974F5PW		92mg
HYDROXYPROPYL CELLULOSE (110000 WAMW)	ORAL	TABLET, ORALLY DISINTEGRATING , DELAYED RELEASE	900464 2	5Y0974F5PW		90mg
HYDROXYPROPYL CELLULOSE (110000 WAMW)	TRANSDERMA L	FILM, EXTENDED RELEASE	900464 2	5Y0974F5PW		6mg
HYDROXYPROPYL CELLULOSE (160000 WAMW)	ORAL	TABLET	900464 2	0A7M0N7SPE		8mg
HYDROXYPROPYL CELLULOSE (160000 WAMW)	ORAL	TABLET, EXTENDED RELEASE	900464 2	0A7M0N7SPE		180mg
HYDROXYPROPYL CELLULOSE (1600000 WAMW)	BUCCAL	FILM	900464 2	RFW2ET671P		87mg
HYDROXYPROPYL CELLULOSE (1600000 WAMW)	ORAL	CAPSULE	900464 2	RFW2ET671P		120mg

HYDROXYPROPYL CELLULOSE (1600000 WAMW)	ORAL	CAPSULE, COATED PELLETS	900464 2	RFW2ET671P	41.4mg	
HYDROXYPROPYL CELLULOSE (1600000 WAMW)	ORAL	CAPSULE, DELAYED RELEASE	900464 2	RFW2ET671P		150mg
HYDROXYPROPYL CELLULOSE (1600000 WAMW)	ORAL	CAPSULE, EXTENDED RELEASE	900464 2	RFW2ET671P		204mg
HYDROXYPROPYL CELLULOSE (1600000 WAMW)	ORAL	GRANULE	900464 2	RFW2ET671P		13mg
HYDROXYPROPYL CELLULOSE (1600000 WAMW)	ORAL	GRANULE, FOR SUSPENSION	900464 2	RFW2ET671P		194mg
HYDROXYPROPYL CELLULOSE (1600000 WAMW)	ORAL	LOZENGE	900464 2	RFW2ET671P		500mg
HYDROXYPROPYL CELLULOSE (1600000 WAMW)	ORAL	POWDER	900464 2	RFW2ET671P		244mg
HYDROXYPROPYL CELLULOSE (1600000 WAMW)	ORAL	POWDER, FOR SUSPENSION	900464 2	RFW2ET671P		200mg
HYDROXYPROPYL CELLULOSE (1600000 WAMW)	ORAL	SUSPENSION	900464 2	RFW2ET671P		40mg
HYDROXYPROPYL CELLULOSE (1600000 WAMW)	ORAL	TABLET	900464 2	RFW2ET671P		230mg
HYDROXYPROPYL CELLULOSE (1600000 WAMW)	ORAL	TABLET, CHEWABLE	900464 2	RFW2ET671P		10mg
HYDROXYPROPYL CELLULOSE (1600000 WAMW)	ORAL	TABLET, COATED	900464 2	RFW2ET671P	13.6mg	

HYDROXYPROPYL CELLULOSE (1600000 WAMW)	ORAL	TABLET, DELAYED RELEASE	9004642	RFW2ET671P		450mg
HYDROXYPROPYL CELLULOSE (1600000 WAMW)	ORAL	TABLET, EXTENDED RELEASE	9004642	RFW2ET671P		864mg
HYDROXYPROPYL CELLULOSE (1600000 WAMW)	ORAL	TABLET, FILM COATED	9004642	RFW2ET671P	131.67mg	
HYDROXYPROPYL CELLULOSE (1600000 WAMW)	ORAL	TABLET, FILM COATED, EXTENDED RELEASE	9004642	RFW2ET671P	187.6mg	
HYDROXYPROPYL CELLULOSE (1600000 WAMW)	ORAL	TABLET, ORALLY DISINTEGRATING	9004642	RFW2ET671P		4mg
HYDROXYPROPYL CELLULOSE (1600000 WAMW)	ORAL	TABLET, ORALLY DISINTEGRATING, DELAYED RELEASE	9004642	RFW2ET671P	39.2mg	
HYDROXYPROPYL CELLULOSE (1600000 WAMW)	SUBLINGUAL	TABLET	9004642	RFW2ET671P	1mg	
HYDROXYPROPYL CELLULOSE (1600000 WAMW)	TOPICAL	GEL	9004642	RFW2ET671P		222mg
HYDROXYPROPYL CELLULOSE (1600000 WAMW)	TOPICAL	LOTION	9004642	RFW2ET671P		6mg
HYDROXYPROPYL CELLULOSE (1600000 WAMW)	TOPICAL	LOTION, AUGMENTED	9004642	RFW2ET671P	0.2%w/w	
HYDROXYPROPYL CELLULOSE (1600000 WAMW)	TOPICAL	SOLUTION	9004642	RFW2ET671P	0.1%w/v	
HYDROXYPROPYL CELLULOSE (1600000 WAMW)	TRANSDERMAL	FILM, EXTENDED RELEASE	9004642	RFW2ET671P	19mg	

HYDROXYPROPYL CELLULOSE (1600000 WAMW)	TRANSDERMAL	GEL	9004642	RFW2ET671P		20mg
HYDROXYPROPYL CELLULOSE (20000 WAMW)	ORAL	CAPSULE, DELAYED RELEASE	9004642	KZQ570MOA5		51mg
HYDROXYPROPYL CELLULOSE (20000 WAMW)	ORAL	TABLET	9004642	KZQ570MOA5		50mg
HYDROXYPROPYL CELLULOSE (20000 WAMW)	ORAL	TABLET, DELAYED RELEASE	9004642	KZQ570MOA5		212mg
HYDROXYPROPYL CELLULOSE (20000 WAMW)	ORAL	TABLET, EXTENDED RELEASE	9004642	KZQ570MOA5		25mg
HYDROXYPROPYL CELLULOSE (20000 WAMW)	ORAL	TABLET, FILM COATED	9004642	KZQ570MOA5		30mg
HYDROXYPROPYL CELLULOSE (20000 WAMW)	ORAL	TABLET, ORALLY DISINTEGRATING	9004642	KZQ570MOA5		3mg
HYDROXYPROPYL CELLULOSE (430000 WAMW)	ORAL	TABLET	9004642	VQ8ZWO78F6		90mg
HYDROXYPROPYL CELLULOSE (430000 WAMW)	ORAL	TABLET, EXTENDED RELEASE	9004642	VQ8ZWO78F6		252mg
HYDROXYPROPYL CELLULOSE (430000 WAMW)	TOPICAL	LOTION, AUGMENTED	9004642	VQ8ZWO78F6		37mg
HYDROXYPROPYL CELLULOSE (430000 WAMW)	TOPICAL	SOLUTION	9004642	VQ8ZWO78F6		200mg
HYDROXYPROPYL CELLULOSE (45000 WAMW)	ORAL	TABLET	9004642	8VAB711C5E		102mg
HYDROXYPROPYL CELLULOSE (45000 WAMW)	ORAL	TABLET, CHEWABLE	9004642	8VAB711C5E		57mg
HYDROXYPROPYL CELLULOSE (45000 WAMW)	ORAL	TABLET, EXTENDED RELEASE	9004642	8VAB711C5E		140mg
HYDROXYPROPYL CELLULOSE (650000 WAMW)	ORAL	TABLET, EXTENDED RELEASE		1L0RPI3ASP		132mg

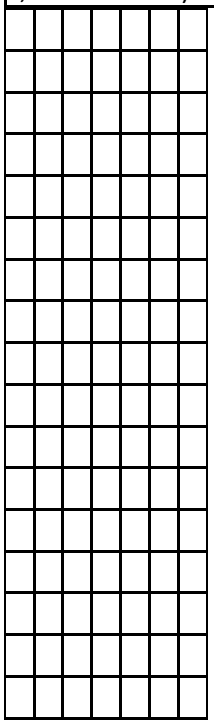
HYDROXYPROPYL CELLULOSE (70000 WAMW)	ORAL	CAPSULE, DELAYED RELEASE	900464 2	66O7AQV0RT		83mg
HYDROXYPROPYL CELLULOSE (70000 WAMW)	ORAL	CAPSULE, EXTENDED RELEASE	900464 2	66O7AQV0RT		23mg
HYDROXYPROPYL CELLULOSE (70000 WAMW)	ORAL	TABLET, FILM COATED	900464 2	66O7AQV0RT		15mg
HYDROXYPROPYL CELLULOSE (90000 WAMW)	BUCCAL	FILM	900464 2	UKE75GEA7F		100mg
HYDROXYPROPYL CELLULOSE (90000 WAMW)	BUCCAL	FILM, SOLUBLE	900464 2	UKE75GEA7F		292mg
HYDROXYPROPYL CELLULOSE (90000 WAMW)	BUCCAL	GUM, CHEWING	900464 2	UKE75GEA7F		670mg
HYDROXYPROPYL CELLULOSE (90000 WAMW)	ORAL	CAPSULE	900464 2	UKE75GEA7F		69mg
HYDROXYPROPYL CELLULOSE (90000 WAMW)	ORAL	CAPSULE, DELAYED RELEASE	900464 2	UKE75GEA7F		114mg
HYDROXYPROPYL CELLULOSE (90000 WAMW)	ORAL	CAPSULE, EXTENDED RELEASE	900464 2	UKE75GEA7F		60mg
HYDROXYPROPYL CELLULOSE (90000 WAMW)	ORAL	GRANULE	900464 2	UKE75GEA7F		3mg
HYDROXYPROPYL CELLULOSE (90000 WAMW)	ORAL	LOZENGE	900464 2	UKE75GEA7F		500mg
HYDROXYPROPYL CELLULOSE (90000 WAMW)	ORAL	POWDER, FOR SUSPENSION	900464 2	UKE75GEA7F		54mg
HYDROXYPROPYL CELLULOSE (90000 WAMW)	ORAL	SUSPENSION	900464 2	UKE75GEA7F		67mg
HYDROXYPROPYL CELLULOSE (90000 WAMW)	ORAL	TABLET	900464 2	UKE75GEA7F		594mg
HYDROXYPROPYL CELLULOSE (90000 WAMW)	ORAL	TABLET, CHEWABLE	900464 2	UKE75GEA7F		19mg

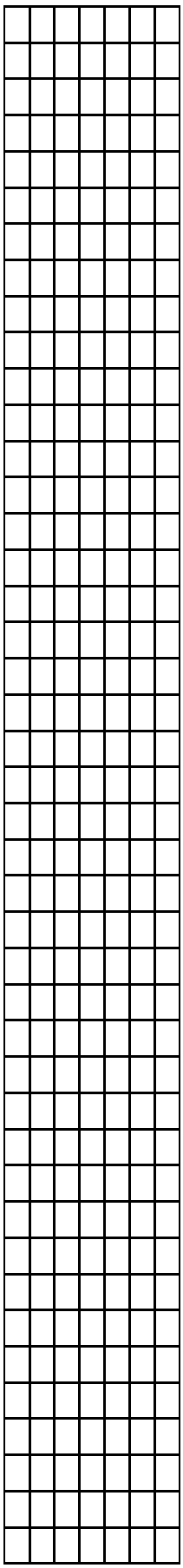
HYDROXYPROPYL CELLULOSE (90000 WAMW)	ORAL	TABLET, COATED	900464 2	UKE75GEA7F		88mg
HYDROXYPROPYL CELLULOSE (90000 WAMW)	ORAL	TABLET, DELAYED RELEASE	900464 2	UKE75GEA7F		630mg
HYDROXYPROPYL CELLULOSE (90000 WAMW)	ORAL	TABLET, EXTENDED RELEASE	900464 2	UKE75GEA7F		364mg
HYDROXYPROPYL CELLULOSE (90000 WAMW)	ORAL	TABLET, FILM COATED	900464 2	UKE75GEA7F		32mg
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE	ORAL	CAPSULE	900464 2	2165RE0K14		150mg
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE	ORAL	TABLET	900464 2	2165RE0K14		480mg
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE	ORAL	TABLET, DELAYED RELEASE	900464 2	2165RE0K14		103mg
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE	ORAL	TABLET, FILM COATED	900464 2	2165RE0K14		40mg
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (11% HYDROXYPROPYL ; 100000 MW)	ORAL	CAPSULE, DELAYED RELEASE	900464 2	BMJ7J4127K		65mg
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (11% HYDROXYPROPYL ; 100000 MW)	ORAL	CAPSULE, EXTENDED RELEASE	900464 2	BMJ7J4127K		141mg
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (11% HYDROXYPROPYL ; 100000 MW)	ORAL	TABLET	900464 2	BMJ7J4127K		54mg

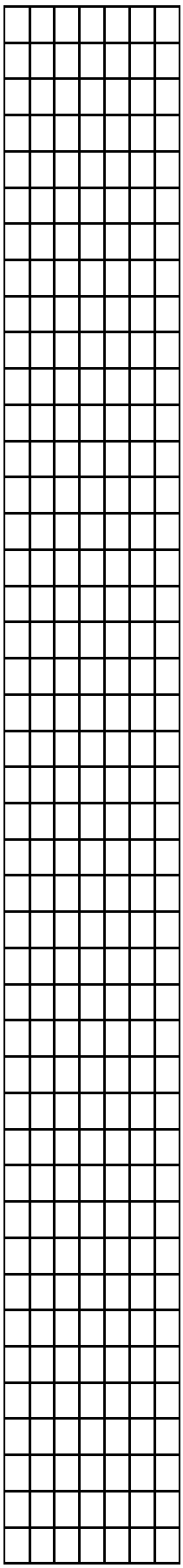
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (11% HYDROXYPROPYL; 120000 MW)	ORAL	CAPSULE	900464 2	NZ94SDL6WR		178mg
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (11% HYDROXYPROPYL; 120000 MW)	ORAL	CAPSULE, DELAYED RELEASE	900464 2	NZ94SDL6WR	40mg	
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (11% HYDROXYPROPYL; 120000 MW)	ORAL	TABLET	900464 2	NZ94SDL6WR		370mg
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (11% HYDROXYPROPYL; 120000 MW)	ORAL	TABLET, CHEWABLE	900464 2	NZ94SDL6WR		70mg
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (11% HYDROXYPROPYL; 120000 MW)	ORAL	TABLET, DELAYED RELEASE	900464 2	NZ94SDL6WR		84mg
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (11% HYDROXYPROPYL; 120000 MW)	ORAL	TABLET, EXTENDED RELEASE	900464 2	NZ94SDL6WR		13mg
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (11% HYDROXYPROPYL; 120000 MW)	ORAL	TABLET, FILM COATED	900464 2	NZ94SDL6WR		210mg
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (11% HYDROXYPROPYL; 120000 MW)	ORAL	TABLET, ORALLY DISINTEGRATING	900464 2	NZ94SDL6WR		60mg

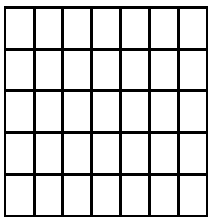
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (11% HYDROXYPROPYL; 130000 MW)	ORAL	CAPSULE	900464 2	7773C1ROEU		200mg
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (11% HYDROXYPROPYL; 130000 MW)	ORAL	CAPSULE, EXTENDED RELEASE	900464 2	7773C1ROEU	16.25mg	
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (11% HYDROXYPROPYL; 130000 MW)	ORAL	TABLET	900464 2	7773C1ROEU		512mg
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (11% HYDROXYPROPYL; 130000 MW)	ORAL	TABLET, CHEWABLE	900464 2	7773C1ROEU		48mg
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (11% HYDROXYPROPYL; 130000 MW)	ORAL	TABLET, DELAYED RELEASE	900464 2	7773C1ROEU		180mg
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (11% HYDROXYPROPYL; 130000 MW)	ORAL	TABLET, DELAYED RELEASE PARTICLES	900464 2	7773C1ROEU		30mg
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (11% HYDROXYPROPYL; 130000 MW)	ORAL	TABLET, FILM COATED	900464 2	7773C1ROEU	50mg	
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (11% HYDROXYPROPYL; 130000 MW)	ORAL	TABLET, FOR SUSPENSION	900464 2	7773C1ROEU		320mg

LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (11% HYDROXYPROPYL ; 130000 MW)	ORAL	TABLET, ORALLY DISINTEGRATING	900464 2	7773C1ROEU		60mg
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (11% HYDROXYPROPYL ; 140000 MW)	ORAL	TABLET		599BTP6K9F		50mg
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (8% HYDROXYPROPYL : 140000 MW)	ORAL	TABLET	900464 2	U466TXA0AK		54mg
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (8% HYDROXYPROPYL ; 120000 MW)	ORAL	CAPSULE, EXTENDED RELEASE	900464 2	R67D5N7LRS		194mg
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (8% HYDROXYPROPYL ; 120000 MW)	ORAL	TABLET, ORALLY DISINTEGRATING , DELAYED RELEASE	900464 2	R67D5N7LRS		120mg









As taken from FDA, 2024c

Hydroxypropylcellulose (CAS RN 9004-64-2) is classified as a “non-NHP” (non-natural health product) because it is “not a naturally occurring substance included in Schedule 1 of the NHP Regulations” (Health Canada, 2021).

4. Metabolism/Pharmacokinetics

4.1. Metabolism/metabolites

The metabolic study has revealed adequate in vivo evidence of the biochemical inertness of hydroxypropyl cellulose and of its non-absorption during passage through the gastro-intestinal tract. This behaviour parallels that of other modified celluloses considered previously. The material studied had the highest dense of hydroxypropyl substitution likely to be used as food additive. (JECFA, 1969).

4.2. Absorption, distribution and excretion

14C-labelled hydroxypropyl cellulose was administered to four rats in a five per cent. aqueous solution. One male and one female rat received 0.25 g/kg body weight, the other two rats received 1 g/kg body weight. Urine, faeces and expired air were collected over the next 120 h. Then all organs were assayed for residual radioactivity. No activity (< 0.01 per cent. of the administered dose) was detected in organs, urine and expired air due to administered material. Recoveries of activity in the faeces varies from 98.32 to 102.7 per cent. Hence orally ingested material is not absorbed from the gastro-intestinal tract of the rat and is excreted quantitatively in the faeces principally in the first 48 h. (JECFA, 1969 & 1989).

To check on enterohepatic circulation two additional rats with ligated bile ducts were administered 1 g/kg of radio-labelled material. Bile was collected for 72 h but no significant activity was found (Industrial Bio-Test Lab., 1964). (JECFA, 1969 & 1989).

[^{14}C]hydroxypropylcellulose (12.28% hydroxypropyl group, 2.74 uCi/mg) was administered to 3 male and 3 female rats of Wistar-Imamichi Strain, weighing approximately 250g, at a dose of 1.3 g/kg bw. Urine and feces were collected for 96 hours, and the residual radioactivity was measured in the tissues of the rats after sacrifice. The bile duct was cannulated for bile collections. The mean urinary excretion of radioactivity over 96 hours was 2.63% inmales and 1.50% in females. The mean fecal excretion was 68.7% and 97.3% in males, and 62.4% and 96.8% in females, over 24 and 96 hrs, respectively. Total radioactivity in urine and feces over 96 hrs was 99.9% in males and 98.3% in females. Cumulative biliary excretion over 24 hrs was .015% for males and .0024% for females (Kitagawa et al., 1976a).

Gel filtration chromatographic patterns of urine were inconclusive for identification of the single peak of radioactivy material. The elution position showed a molecular weight slightly higher than glycerol or glucose and it was found at a different position than propylene glycol, which was present at a level of less than 2% in the administered material. No radioactivity was detectable in tissues other than the liver and kidney. The highest radioactivity in the liver was 1.5% of the dose in male rats at 12 hrs and 0.026% at 24 hrs in females (Kitagawa et al., 1976a). (JECFA, 1989).

“Chemically modified celluloses are not absorbed intact nor fermented, but are excreted intact via the faeces.”

As taken from EFSA, 2018a.

“Groups of three young male and three young female Sprague–Dawley rats were dosed with 500 mg/kg bw per day of 14C-HPMC (viscosity of 2.25 cP) once or once daily over five consecutive days via gavage (Gorzinski et al., 1986). After single dosing, about 73-101% of the applied dose was excreted within 24 h via faeces (100-105% within 72 h), while within 72 h only up to 1.5% was found in urine, 0.2% in carcass and tissues and 0.07% in expired air. In bile, a collection over 24 h in two male rats gave 0.05% of the applied dose. In plasma, the elimination of radioactivity was monophasic, with a half-live of about 2 h. Most of the residual radioactivity was found in the GI tract (no details given). In urine, methyl ethers of glucose and oligomers were identified, determined by thin layer chromatography in 6-h urine from one animal of each sex. Also, after dosing once daily over 5 days, most of the applied dose was excreted via faeces (97-104%), while only 1% was recovered in urine. There was no evidence of accumulation in the tissues examined (adrenals, brain, heart, liver, kidneys and spleen). A determination in exhaled air was not performed.”

“In a study with 25 young and healthy adults (23 males and 2 females), each person was given 3 graduated doses of HPMC ranging from 0.6 to 8.9 g (Knight et al., 1952). The time interval between the doses was at least 1 week. Following each dose, stool specimens were collected at approximately 24-h intervals for 72 or 96 h. For a determination of the quantitative amounts of HPMC in the samples of dried faeces, an analytical procedure, consisting of a methoxyl determination made directly on the faeces samples, was used. Nearly all of the ingested substance (average of total recovery 97%, with a range of 89-110%) was excreted via faeces within 96 h following administration.”

As taken from EFSA, 2018b

“The EFSA ANS Panel (2018) concluded that modified celluloses including ethyl, methyl, hydroxypropyl celluloses, would not be absorbed intact and not fermented in the gastrointestinal tract of animals (rat) or humans; they are excreted essentially unchanged mainly via the faeces (more than 90% of the administrated doses), while only minor amounts of metabolites and derived-products are excreted via urine or expired air (as $^{14}CO_2$) and there is no indication for accumulation in the body.”

As taken from EFSA, 2020

4.3. Interactions

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). (CIR 2009)

“Despite the numerous advantages of powder formulations, few studies have described their nasal drug absorption. The first aim of this study was to compare the drug absorption from powder formulation with that from a liquid formulation in rats. Since pharmaceutical excipients are usually added to most powder formulations, the second aim of the study was to investigate the effect of hydroxypropyl cellulose (HPC) on nasal drug absorption from the powder. Three types of HPC with different polymerization degrees were used: HPC(SL), HPC(M), and HPC(H). The model drugs were warfarin (BCS Class I), piroxicam (BCS Class II), and sumatriptan (BCS Class III). The absorption of these model drugs in the powder form was higher than that from the solution. All HPCs failed to enhance warfarin absorption, while the piroxicam absorption was enhanced only by HPC(M). Sumatriptan absorption was not enhanced by HPC(SL), but by HPC(M) and HPC(H). The differences in nasal absorption of the three model drugs promoted by HPCs depend on the permeability and solubility of the drug. Moreover, the nasal retention of different formulations was increased by HPCs. Because HPCs showed no toxic effect on the nasal epithelium. These findings

indicate that powder formulations supplemented with HPC are a valuable and promising approach to increase the nasal absorption of highly soluble and poorly permeable drugs." As taken from Tanaka A et al. 2017. Eur. J. Pharm. Sci. 96, 284-289. PubMed, 2018 available at https://www.ncbi.nlm.nih.gov/pubmed/27664332

"Herein, we report novel macromolecular prodrugs (MPDs) of flurbiprofen (FLB) onto a cellulose ether, hydroxypropylcellulose (HPC). The FLB was activated with a powerful acylation reagent carbonyldiimadazole (CDI) in N,N' dimethylacetamide (DMAc) solvent at room temperature. Imidazolide of FLB generated in situ reacts at 80 °C for 24 h with pre-dissolved HPC to prepare HPC-FLB conjugates. The resultant MPDs of FLB showed moderate to high degree of substitution (DS: 0.35-1.3) with good yield (70-82%). Structures were thoroughly characterized using FTIR, UV and NMR spectroscopic analyses. The pharmacokinetic studies showed that the t1/2 and tmax values of FLB from HPC-FLB conjugate were increased substantially as compare to standard FLB indicates enhanced bioavailability of drug after conjugate formation. Remarked anti-inflammatory activity of the HPC-FLB conjugate was also observed." As taken from Hussain MA et al. 2020. Saudi Pharm. J. 28(7), 869-875. PubMed, 2020 available at https://pubmed.ncbi.nlm.nih.gov/32647489/

"Hydroxypropyl-cellulose (HPC) is a surface-active, non-digestible polysaccharide, commonly used in food emulsions as thickener and/or emulsifier. Due to these dual characteristics, HPC is a potential ingredient to modulate lipid digestion. Since bile salts (BS) are key players during lipid digestion, the aim of this work was to investigate the impact that interactions of HPC with BS has on the digestion of emulsified lipids. We studied the effect of two BS species differing in bile-acid moiety, sodium-taurocholate (NaTC) and sodium-taurodeoxycholate (NaTDC). A Quartz-Crystal-Microbalance (QCM-D) was used to evaluate HPC-BS interfacial interactions during the sequential and simultaneous adsorption of both components at a hydrophobic surface, while micro-Differential-Scanning-Calorimetry was used to examine bulk interactions. In vitro lipid digestion was studied by using a pH-stat method. Results showed that, under fed-state conditions, NaTDC micelles were more effective at displacing a pre-adsorbed HPC layer from the surface than NaTC monomers. Nevertheless, HPC was resistant to complete displacement by both BS. Additionally, HPC was more susceptible to interact with NaTDC in the bulk, compared to NaTC, which made the adsorption more competitive for NaTDC. The reduced amount of free NaTDC in solution could explain the delayed lipolysis shown by HPC-stabilized emulsions when NaTDC was used to simulate duodenal conditions. These findings show that the delay of lipid digestion by HPC is due to the combined effect of HPC-BS interfacial and bulk interactions, with BS-binding in solution mostly contributing to this effect, and the BS molecular and micellar structure playing essential roles on both situations." As taken from Zornjak J et al. 2020. Food Hydrocolloids 106, 105867. Available at https://www.sciencedirect.com/science/article/pii/S0268005X1932507X

5. Toxicity

5.1. Single dose toxicity

Organism	Test Type	Route	Reported Dose (Normalized Dose)	Effect	Source
mouse	LD50	intraperitoneal	> 25gm/kg (25000mg/kg)		Oyo Yakuri. Pharmacometrics. Vol. 4, Pg. 1013, 1970.
mouse	LD50	intravenous	> 500mg/kg (500mg/kg)		Oyo Yakuri. Pharmacometrics. Vol. 4, Pg. 1013, 1970.
mouse	LD50	oral	> 5gm/kg (5000mg/kg)		Oyo Yakuri. Pharmacometrics. Vol. 4, Pg. 1013, 1970.

rat	LD50	intraperitoneal	> 25gm/kg (25000mg/kg)		Oyo Yakuri. Pharmacometrics. Vol. 4, Pg. 1013, 1970.
rat	LD50	intravenous	250mg/kg (250mg/kg)		Oyo Yakuri. Pharmacometrics. Vol. 4, Pg. 1013, 1970.
rat	LD50	oral	10200mg/kg (10200mg/kg)		FAO Nutrition Meetings Report Series. Vol. 46A, Pg. 131, 1969.

As taken from RTECS, 2010

Low, middle, and high viscosity Hydroxypropylcellulose solutions (aqueous) had oral LD50s > 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 LD50 was defined as > 15 g/kg Hydroxypropylcellulose (Kitigawa et al.1 9 7 6) . (CIR 2009).

A conditioning polish remover containing 0 .7% Hydroxypropylcellulose had an acute oral LD50 of 10.1 ml/kg (or 8.2 g/kg) in rats (Stillmeadow 1977). (CIR 2009)

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). (CIR 2009).

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). (CIR 2009)

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). (CIR 2009).

5.2. Repeated dose toxicity

Groups of five male and five female rats received in their diet 0.2 per cent., 1.0 per cent. and 5.0 per cent, of hydroxypropyl cellulose for 90 days. Controls received unmodified cellulose at the same levels. There were no differences observed between tests and controls as regards mortality, growth, food utilization, urinalysis, haemotological indices, organ weight, gross pathology and histopathology. At higher dietary levels there was increased food consumption and decreased food utilization consequential to the inertness of the material (Industrial Bio-Test Lab., 1963). (JECFA, 1969 & 1989).

Groups of 10 male and 10 female young adult Wistar rats were fed hydroxypropyl cellulose in 1% gum arabic at doses of 0, 1.5, 3.0, or 6.0 g/kg bw/day for 30 days and for 6 months. After 30 days, no effects were observed on body weight and food consumption, serum chemistry, urinalysis, or histopathology. In females, liver, kidney and brain weights were decreased at 3.0 g/kg bw/day, but the decrease did not show a consistent dose-response relationship. After 6 months, decreased body weight was noted at the high dose level, which was statistically significant for females. No effects related to dosage were noted on food consumption, serum chemistry, urinalysis, or histopathology. The hemoglobin level of male high- and mid-dose rats was reduced. There were sporadic increases or decreases in organ weights of a few groups without a dose relationship or associated pathological change (Kitigawa et al., 1976b). (JECFA 1989)

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). (CIR 2009).

Species	Route	Duration	Dose	Adverse reactions/toxicity	Data source
Rat	PO, oral	90 days	1,000 g/kg	Well tolerated	Gad et al.

As taken from Gad et al., 2016

POD Method	**POD Value**	**POD Owner**
HNEL	Not Calculated	PAFA

Lowest-observed effect

Owner	**Type**	**Value**	**Sites**	**Effects**
PAFA	LOAEL	6000.0 mg/kg bw/day	BODY WEIGHT CHANGES	BODY WEIGHT CHANGES

No-observed effect: PAFA: HNEL: 3000.0 mg/kg bw/day

Adjustment factors: Critical study: Target Organ Toxicity > Chronic Toxicity (Rat, Oral - Dietary exposure) for 180 day

As taken from COSMOS Database. Accessed September 2021“For hydroxypropyl cellulose (E 463), the identified NOAEL corresponded to the highest dose 6,000 mg hydroxypropyl cellulose/kg bw and day (by gavage).”

“In the only identified study, the daily dosing of male and female rats (0, 1,500, 3,000 or 6,000 mg hydroxypropyl cellulose/kg bw) via gavage for 6 months did not cause adverse effects (including carcinogenicity) apart from a decrease in body weight in high-dosed rats (statistically significant in females only).”

As taken from EFSA, 2020

5.3. Reproduction toxicity

Groups of nulliparous female Wistar rats were mated to give 36-37 pregnant rats per dose group. Hydroxypropyl cellulose was administered daily by gavage in 1% gum arabic at dose levels of 0, 200, 1000, or 5000 mg/kg bw/day between days 7 and 17 post-mating. On day 21 of gestation, 21-24 females were subjected to Cesarean section. Corpora lutea, implantations, viable and dead fetuses, and resorbed embryos were counted and positions of implantations were observed. All viable fetuses were individually weighed and examined for abnormalities. Two to three fetuses per group were examined for skeletal abnormalities, and the remainder were examined for visceral abnormalities. Twelve to fifteen dams were allowed to deliver spontaneously. Viable pups and stillborns were counted, and records taken of body weight, sex, and presence of external anomalies. General behavior of pups was observed during nursing and individual body weights were recorded at delivery and weaning. Times for separation of lower incisors and and separation of eyelids were noted. The pups were weaned at the 28th day after birth. Each weanling was examined for general behavior and nervous reflexes. Skeletal examination was done by soft X-ray. One male and one female per group were killed and wet weights of the brain, heart, lung, liver, spleen, kidney, thymus, adrenal, testes, epididymis, prostate, ovary, pituitary and thyroid were

obtained. Remaining weanlings were observed for 5 weeks for body weight gain, and at maturity for conditioned avoidance response and reproductive ability.

Both mean litter weight and percent pre-implantation loss were significantly increased in the high dose group. The percent of skeletal variations was significantly increased for the mid dose only. At maturity, the progeny showed no effects on reflex behavior or reproductive ability (Kitagawa et al., 1978a). (JECFA 1989)

Groups of 11-12 pregnant Himalayan rabbits received oral doses of hydroxypropyl cellulose by gavage in 1% gum arabic at levels of 0, 200, 1000, or 5000 mg/kg bw daily from days 6-18 of pregnancy. Cesarean sections were performed on the 29th day of pregnancy and all fetuses were examined for skeletal and organ malformations. Up to the 18th day of study a slight body weight loss was noted in the high dose group. A slight decrease in the number of implants, not dose-related, was recorded in treatment groups. The resorption rate was significantly decreased only in the intermediate dosage group. The mean fetal viable weight was not different between groups. The pre-implantation loss was significantly increased in the 5000 mg/kg bw/day group. The incidence of malformations was comparable to historical controls and was not dose-related (Kitagawa et al., 1978b). (JECFA 1989)

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. (CIR 2009)

“The only relevant developmental toxicity study with hydroxypropyl cellulose (E 463) (dissolved in 1% gum arabic solution) was performed in pregnant rats exposed via gavage from day 7 to 17 of gestation to 0, 200, 1,000 or 5,000 mg/kg bw test item and some of them subjected to caesarean sections at day 20. No treatment-related adverse effects were detected in dams or in the examined fetuses. A number of dams were allowed to deliver and no clinical, behavioural or morphological changes were observed in the examined pups. Their reproductive ability was seemingly not affected and no abnormalities were found in the F1-derived fetuses.”

As taken from EFSA, 2020

5.4. Mutagenicity

“The Ministry of Health, Labour and Welfare has carried out genotoxicity tests for food additives used in Japan in cooperation with the Japan Food Additives Association since 1979. Hayashi et al. summarized these data and published a list of 337 designated additives (Shitei-tenkabutsu in Japanese) with genotoxicity test data in 2000. Thereafter, 29 items were eliminated, and 146 items were newly added. Currently, 454 designated additives are allowed to be used as food additives in Japan. This report, based on the Hayashi report, covers the addition of newly derived genotoxicity test data. Routinely, the bacterial reverse mutation test (Ames test), mammalian cell chromosomal aberration test, and in vivo rodent bone marrow micronucleus test have been used for the evaluation of genotoxicity of food additives. In addition to the data from these tests being updated in this report, it newly includes results of transgenic rodent somatic and germ cell gene mutation assays (TGR assays), incorporated in the Organisation for Economic Co-operation and Development (OECD) test guidelines after 2000. We re-evaluated the genotoxicity of 13 designated food additives considering their TGR data.” As taken from Yamada M and Honma M. 2018. Genes Environ. 40, 27. PubMed, 2019 available at https://www.ncbi.nlm.nih.gov/pubmed/30619512

“[I]t should be considered that the chemical structure of unmodified and modified cellulose does not show any alert for genotoxicity and that no indication of genotoxicity was found for any of these substances in several in vitro and in vivo genotoxicity studies.”

“Based on the available experimental data, neither microcrystalline cellulose nor modified cellulose raise concern for genotoxicity.”

As taken from EFSA, 2020

5.5. Cytotoxicity

No data available to us at this time.

5.6. Carcinogenicity

“There was no indication for carcinogenic effects for all tested compounds [including hydroxypropyl cellulose].”

As taken from EFSA, 2020

5.7. Irritation/immunotoxicity

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). (CIR 2009).

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 wereadministered 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 AOIIs 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). (CIR 2009).

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). (CIR 2009).

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). (CIR 2009).

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). (CIR 2009).

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 (31group) 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

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. PIIs 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).

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. Overall, these ingredients are non-irritating and are nonsensitizing. (CIR 2009)

5.8. All other relevant types of toxicity

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). (CIR 2009)

6. Functional effects on

6.1. Broncho/pulmonary system

No data available to us at this time.

6.2. Cardiovascular system

No data available to us at this time.

6.3. Nervous system

No data available to us at this time.

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

”In a clinical trial, patients (aged 18 years or more) with chronic watery diarrhoea, presumably secondary to idiopathic bile acid malabsorption, were randomly assigned to two groups given either colestyramine (n=13, 7 females/6 males) or HPC (n=13, 11 females/2 males) (Fernandez-Banares et al., 2015). Both substances were given in the form of 4 g sachets twice daily for 8 weeks. The Panel noted that the two adverse effects (muscle pain, nasopharyngitis) observed in the HPC group seem not to be associated with the intake of HPC, thus HPC is considered to be well tolerated in doses of two or three 4 g sachets per day.”

”Wyatt et al. (1988) compared the effect of a fibre-free diet and of diets containing non-digestible polysaccharides, including HPMC, on rat caecal and colonic physiology and micro flora. All polysaccharide-containing diets led to enlargement of the caecum and colon, associated with

increased weight of contents and tissue. In vitro, HPMC remained almost completely unfermented, with only 5% of the substrate utilised after 7 days of incubation. According to the authors, caecal and colonic enlargement would be due to tissue hypertrophy in response to increased bulk of contents, irrespective of the nature of that bulk, which varies with diet. It would be unlikely that SCFA or other microbial metabolites are the stimulus for the trophic response seen when non-digestible dietary polysaccharides are fed to rats."

As taken from EFSA, 2018b

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

Aerosol from an electronic nicotine delivery system (ENDS) product that creates a vapor by heating an e-liquid; the vapor then passes through a capsule containing tobacco granules, containing Hydroxypropylcellulose was tested in a battery of in vitro and/or in vivo test(s). Under the test conditions and within the sensitivity and specificity of the bioassay(s), no mutagenic, genotoxic or cytotoxic responses were observed when exposed to Aerosol Collected Matter (ACM) and/or aerosol Gas Vapor Phase (GVP) and no adverse findings from a 90-day in vivo repeat-dose inhalation toxicity study were observed after exposure to the aerosol even when exposure concentrations were the maximal amount that could be achieved with the specific product(s). These results are in contrast to those observed with combustible cigarette which showed mutagenic, genotoxic, cytotoxic and adverse effects upon exposure. The table below provides tested level(s) and specific endpoint(s):

Endpoint	Tested level	Reference
Aerosol chemistry	17.4733 mg/(tobacco portion; 310 mg)	Logic (2019)
In vitro genotoxicity	17.4733 mg/(tobacco portion; 310 mg)	Logic (2019)
In vitro cytotoxicity	17.4733 mg/(tobacco portion; 310 mg)	Logic (2019)
In vivo genotoxicity	17.4733 mg/(tobacco portion; 310 mg)	Logic (2019)
Inhalation study	17.4733 mg/(tobacco portion; 310 mg)	Logic (2019)

Aerosol from heated tobacco stick(s) containing Hydroxypropylcellulose was tested in aerosol chemistry and a battery of in vitro test(s). Under the test conditions and within the sensitivity and specificity of the bioassay(s), the activity of the total particulate matter (TPM) and/or gas vapor phase (GVP) were not increased by the addition of this ingredient when compared to TPM and/or GVP from reference combustible cigarettes. The table below provides the highest tested level(s) and specific endpoint(s):

Endpoint	Tested level (mg/stick)	Reference
Aerosol chemistry	1.35	Labstat International Inc. (2021a) Labstat International Inc. (2023a) JTI Heated Tobacco Stick Study Report(s)

In vitro genotoxicity	1.35	Labstat International Inc. (2021b) Labstat International Inc. (2023b) JTI Heated Tobacco Stick Study Report(s)
In vitro cytotoxicity	1.35	Labstat International Inc. (2021b) Labstat International Inc. (2023b) JTI Heated Tobacco Stick Study Report(s)

10. Ecotoxicity

10.1. Environmental fate

No data available to us at this time.

10.2. Aquatic toxicity

No data available to us at this time.

10.3. Sediment toxicity

No data available to us at this time.

10.4. Terrestrial toxicity

No data available to us at this time.

10.5. All other relevant types of ecotoxicity

No data available to us at this time.

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12. Other information

No data available to us at this time.

13. Last audited

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SCIENTIFIC OPINION

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Re-evaluation of celluloses E 460(i), E 460(ii), E 461, E 462, E 463, E 464, E 465, E 466, E 468 and E 469 as food additives

EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), Maged Younes, Peter Aggett, Fernando Aguilar, Riccardo Crebelli, Alessandro Di Domenico, Birgit Dusemund, Metka Filipič, Maria Jose Frutos, Pierre Galtier, David Gott, Ursula Gundert-Remy, Gunter Georg Kuhnle, Claude Lambré, Jean-Charles Leblanc, Inger Therese Lillegaard, Peter Moldeus, Alicja Mortensen, Agneta Oskarsson, Ivan Stankovic, Paul Tobback, Ine Waalkens-Berendsen, Matthew Wright, Alexandra Tard, Stavroula Tasiopoulou and Rudolf Antonius Woutersen

Abstract

Following a request from the European Commission, the EFSA Panel on Food Additives and Nutrient sources added to Food (ANS) was asked to deliver a scientific opinion on the re-evaluation of microcrystalline cellulose (E 460(i)), powdered cellulose (E 460(ii)), methyl cellulose (E 461), ethyl cellulose (E 462), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464), ethyl methyl cellulose (E 465), sodium carboxy methyl cellulose (E 466) and enzymatically hydrolysed carboxy methyl cellulose (E 469) as food additives. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the Scientific Committee on Food (SCF) established an acceptable daily intake (ADI) 'not specified' for unmodified and modified celluloses. Celluloses are not absorbed and are excreted intact in the faeces; in addition, microcrystalline cellulose, powdered and modified celluloses could be fermented by the intestinal flora in animals and humans. Specific toxicity data were not always available for all the celluloses evaluated in the present opinion and for all endpoints. Given their structural, physicochemical and biological similarities, the Panel considered it possible to read-across between all the celluloses. The acute toxicity of celluloses was low and there was no genotoxic concern. Short-term and subchronic dietary toxicity studies performed with E 460(i), E 461, E 462, E 463, E 464, E 466 and E 469 at levels up to 10% did not indicate specific treatment related adverse effects. In chronic toxicity studies performed with E 460(i), E 461, E 463, E 464, E 465 and E 466, the no observed adverse effect level (NOAEL) values reported ranged up to 9,000 mg/kg body weight (bw) per day. No carcinogenic properties were detected for microcrystalline cellulose and modified celluloses. Adverse effects on reproductive performance or developmental effects were not observed with celluloses at doses greater than 1,000 mg/kg bw by gavage (often the highest dose tested). The combined exposure to celluloses (E 460–466, E 468 and E 469) at 95th percentile of the refined (brand-loyal) exposure assessment for the general population was up to 506 mg/kg bw per day. The Panel concluded that there was no need for a numerical ADI and that there would be no safety concern at the reported uses and use levels for the unmodified and modified celluloses (E 460(i); E 460(ii); E 461–466; E 468 and E 469). The Panel considered an indicative total exposure of around 660–900 mg/kg bw per day for microcrystalline, powdered and modified celluloses.

Keywords: Microcrystalline cellulose (E 460(i)), powdered cellulose (E 460(ii)), methyl cellulose (E 461), ethyl cellulose (E 462), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464), ethyl methyl cellulose (E 465), sodium carboxy methyl cellulose (E 466), cross-linked carboxy methyl cellulose (E 468), enzymatically hydrolysed carboxy methyl cellulose (E 469)

Requestor: European Commission

Question numbers: EFSA-Q-2011-00545, EFSA-Q-2011-00546, EFSA-Q-2011-00547, EFSA-Q-2011-00548, EFSA-Q-2011-00551, EFSA-Q-2011-00549, EFSA-Q-2011-00550, EFSA-Q-2011-00552, EFSA-Q-2011-00553, EFSA-Q-2011-00554

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Summary

Following a request from the European Commission, the EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) was asked to deliver a scientific opinion re-evaluating the safety of microcrystalline cellulose (E 460(i)), powdered cellulose (E 460(ii)), methyl cellulose (E 461), ethyl cellulose (E 462), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464), ethyl methyl cellulose (E 465), sodium carboxy methyl cellulose (E 466), enzymatically hydrolysed carboxy methyl cellulose (E 469) and cross-linked carboxy methyl cellulose (E 468) as food additives. These celluloses are authorised as food additives in accordance with Annex II and Annex III of Regulation (EC) No 1333/2008.

Cellulose is a linear glucose homopolymer consisting of glucopyranose units linked by β-1,4-glycosidic bonds; its molecular formula is $(C_6H_{10}O_5)_m$, with the degree of polymerisation (DP) dependent on the origin of the cellulolytic material. Cellulose molecular weight has been calculated to be approximately in the range 50,000–2,500,000. In modified celluloses, the chemical and physical characteristics of the native substances are modified in order to confer different technological properties for particular food applications.

Microcrystalline cellulose is purified, partially depolymerised cellulose prepared by treating α-cellulose, obtained as a pulp from strains of fibrous plant material, while powdered cellulose is purified, mechanically disintegrated cellulose prepared by processing α-cellulose.

Methyl cellulose (E 461), ethyl cellulose (E 462), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464) and ethyl methyl cellulose (E 465) are celluloses obtained synthetically from fibrous plant material. Each of the celluloses is partially etherified with methyl groups, ethyl groups, hydroxypropyl groups and contains a small degree of hydroxypropyl substitution, and methyl and ethyl groups, respectively.

Microcrystalline cellulose (E 460(i)) and powdered cellulose (E 460(ii)) have been previously evaluated by the Scientific Committee on Food (SCF), the most recent evaluation dating in 1999. In 1999, the SCF assessed additional toxicological data and confirmed the 'ADI not specified', established in 1978. As a matter of precaution, the Committee repeated the advice given in 1995, according to which, the particle size should not be lower than 5 μm with a tolerance of 10% by the number of particles.

The latest evaluation of methyl cellulose (E 461), ethyl cellulose (E 462), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464), methyl ethyl cellulose (E 465), carboxy methyl cellulose (E 466) by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was done in 1989 (JECFA, 1990), where an acceptable daily intake (ADI) 'not specified' was established for each modified cellulose. Latest evaluation of enzymatically hydrolysed carboxy methyl cellulose (E 469) was done in 1998 (JECFA, 1999a,b) and an ADI 'not specified' was established. The ADI for cross-linked sodium carboxy methyl cellulose previously established by JECFA (2003) is 'not specified' based on the substance being poorly absorbed and of low toxicity, with which is in agreement with the known low toxicity of other modified celluloses.

Animal and human data clearly demonstrated that microcrystalline cellulose (E 460(i)) and powdered cellulose (E 460(ii)) are not absorbed intact in the gastrointestinal tract and could be fermented during their passage through the large intestine by strains of bacteria found in the human colon. Data for methyl cellulose (E 461), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464), ethyl methyl cellulose (E 465), sodium carboxy methyl cellulose (E 466), cross-linked sodium carboxy methyl cellulose (E 468) and enzymatically hydrolysed carboxy methyl cellulose (E 469) demonstrated that these modified celluloses are not absorbed intact, not fermented and are excreted intact via the faeces. The Panel noted that microcrystalline, powdered and modified celluloses would not be absorbed intact and would be less fermented than other polysaccharides such as gums, starches or pectins.

Specific toxicity data were not always available for all the celluloses evaluated in the present opinion and for all endpoints. In general, the most complete data sets were available for microcrystalline cellulose (E 460(i)) and sodium carboxy methyl cellulose (E 466). However, given their structural, physicochemical and biological similarities, the Panel considered it possible to read-across between all the celluloses.

Data on acute oral toxicity are available for microcrystalline cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose and sodium carboxy methyl cellulose. These indicate a low oral acute toxicity.

Short-term and subchronic toxicity studies have been performed with microcrystalline cellulose (E 460(i)), methyl cellulose (E 461), ethyl cellulose (E 462), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464), sodium carboxy methyl cellulose (E 466) and enzymatically

hydrolysed carboxy methyl cellulose (E 469). In the majority of studies, animals were dosed via diet at levels up to 10%. Effects on body weight at the highest dose tested (10%) were reported in some, but not all studies, which may reflect nutritional constraints rather than toxicity. No adverse effects were reported with most of the tested celluloses, except for local effects on caecal size due to the presence of undigested fibre. Groups of 20 Albino Wistar outbred rats per sex were dosed with carboxy methyl cellulose (E 466) or enzymatically hydrolysed carboxy methyl cellulose (E 469) via diet with 0%, 2.5%, 5% and 10% (up to 6,800 mg/kg body weight (bw) per day) for up to 102 days. Effects on caecal weight, urothelial hyperplasia, pelvic nephrocalcinosis, corticomedullary nephrocalcinosis and increased incidence of diffuse epithelial hyperplasia in the urinary bladder were observed. However, the findings in kidneys and urinary bladder were attributed to the concentration of sodium, which was up to fourfold higher in the test diet compared with the basal diet. The Panel noted that this was a plausible explanation for the reported findings.

Avicel® RCN-15 (a mixture of 85% microcrystalline cellulose with 15% guar gum) did not induce mutagenic effects in the presence or absence of a metabolic activation system in bacterial reverse mutation assays (Batt, 1992), in a gene mutation assay in mouse lymphoma cells (at thymidine kinase locus) (Cifone, 1992), in an *in vitro* test for unscheduled DNA synthesis (McKeon, 1992) and in the mouse bone marrow micronucleus assays (Murli, 1992). Negative results were also reported with other microcrystalline cellulose preparations in other unpublished studies (Documentation provided to EFSA no. 34, 35, 36, 37). Overall, the Panel concluded that microcrystalline cellulose (E 460(i)) and powdered cellulose (E 460(ii)), which only differs for polymerisation degree, do not raise concern for genotoxicity.

Concerning methyl cellulose and sodium carboxy methyl cellulose, both substances were negative in Ames tests with different *Salmonella* Typhimurium strains, both with and without metabolic activation (Litton Bionetics Inc., 1975, 1980, Blevins and Taylor, 1982; Ishidate et al., 1984). Negative results were also obtained in a chromosomal aberration assay in Chinese hamster fibroblasts (CHL) (Ishidate et al., 1984), only performed without metabolic activation, and in host-mediated assays with yeast and bacteria (Litton Bionetics Inc., 1974, 1975).

Methyl cellulose was also tested with negative results in an *in vitro* chromosomal aberration assay in human embryonic lung cells (WI-38), and *in vivo* in a chromosome aberration assay in rat bone marrow and in the dominant lethal assay in male rats (Litton Bionetics Inc., 1974).

Therefore, the Panel concluded that methyl cellulose and sodium carboxy methyl cellulose do not raise concern for genotoxicity.

The Panel also considered that read-across from methyl cellulose (E 461) to the other modified celluloses bearing similar simple substituents (E 462, E 463, E 464, E 466) was scientifically justified, and supported by the *in silico* analysis, which did not highlight additional structural alerts for genotoxicity, and concluded that either these modified celluloses did not raise genotoxic concern. Similarly, the Panel considered scientifically justified the read-across from sodium carboxy methyl cellulose (E 466) to its products of enzymatic hydrolysis (E 469) or cross-linking (E 468), which do not bear additional structural determinants of genotoxicity. Overall, the Panel concluded that microcrystalline and powdered cellulose (E 460(i) and E 460(ii)) and modified celluloses (E 461–E 469) do not raise concern for genotoxicity.

Chronic toxicity studies have been performed with microcrystalline cellulose (E 460(i)), methyl cellulose (E 461), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464), ethyl methyl cellulose (E 465) and sodium carboxy methyl cellulose (E 466). Although there were some inconsistencies in the data, the main effects seen were decreases in body weight gain at the highest dose, which are likely to be due to the amount/bulk of celluloses in the diet leading to nutritional imbalance. Furthermore, in a chronic feeding study with microcrystalline cellulose (E 460(i)), some dystrophic calcification of renal tubules was observed in the high dose group (15,000 mg/kg bw per day). The no observed adverse effect level (NOAEL) values reported ranged up to 9,000 mg/kg bw per day. The Panel concluded that microcrystalline cellulose and modified celluloses have no carcinogenic properties and that there was no reason to expect carcinogenic properties with powdered cellulose (E 460(ii)).

Concerning reproductive and developmental toxicity, data are available for microcrystalline cellulose (E 460(i)), methyl cellulose (E 461), hydroxypropyl cellulose (E 463) and sodium carboxy methyl cellulose (E 466). The substances were tested in mice, rats, hamsters and/or rabbits with oral dosing via gavage (FDLI, 1973, 1975; Ferch, 1973a,b; Cannon Labs, 1975, 1977; Kitagawa et al., 1978a,b; Fritz and Becker, 1981; Freeman, 1992b). Adverse effects on reproductive performance or

developmental effects were not observed with modified and unmodified celluloses at doses greater than 1,000 mg/kg bw by gavage (often the highest dose tested).

Specific toxicity data were not always available for all the celluloses for all endpoints. In general, the most complete data sets were available for microcrystalline cellulose (E 460(i)) and sodium carboxy methyl cellulose (E 466). Given the similarities in their structure, relevant physicochemical, metabolic and toxicological properties, the Panel considered it possible to read-across between all the celluloses.

In addition, the Panel noted that methyl cellulose (E 461) and sodium carboxy methyl cellulose (E 466) were frequently used in the formulations for administration of xenobiotics by gavage in chronic, reproductive and developmental toxicity and carcinogenicity studies. In these studies, there should be a negative control group receiving the formulation alone. Although modified cellulose levels were usually only up to 2%, given the number of studies and group sizes in these studies, the overall number of animals tested would be very large. The Panel considered that the absence of reported adverse effects from such vehicle control groups provided additional evidence of the lack of safety concern for modified celluloses at levels up to 2% in the vehicle.

There was evidence that repeated doses up to 35 g/person of microcrystalline cellulose or powdered cellulose did not adversely affect clinical chemistry and haematological parameters and had no effect on the absorption and/or the metabolism of dietary constituents.

Some modified celluloses have been used in patients suffering from diarrhoea or constipation. In general, it can be concluded that an oral ingestion of up to 6,000 mg/person per day for 8 months was well tolerated.

The Panel noted that carboxy methyl cellulose was one of the food additives reported to alter the gut microbiota, promote gut inflammation, promote obesity and to impair glycaemic control in mice (Chassaing et al., 2015). In several studies, other emulsifiers have been reported to alter the gut microbiota, promote gut inflammation, promote obesity and to impair glycaemic control in experimental studies with animals (Swidsinski et al., 2009a,b; Renz et al., 2012; Merga et al., 2014; Cani and Everard, 2015; Chassaing et al., 2015; Romano-Keeler and Weitkamp, 2015; Lecomte et al., 2016; Shah et al., 2017).

Some of the effects associated with emulsifiers are not systematically studied as specific endpoints in toxicity studies performed according to current toxicity testing guidelines; therefore, they would have be investigated on a case-by-case basis if indicated by the results of the general toxicity testing, as recommended in the Guidance for submission of food additives (EFSA ANS Panel, 2012).

The Panel considered that based on the animal data, the toxicity of microcrystalline, powdered and modified celluloses was low and that NOAELs were generally the highest dose tested (up to at least 9,000 mg/kg bw per day). In addition, the large cumulative group of exposed animals from use in control populations to 2% would indicate that there. There were no reasons why humans would be expected to be more sensitive than animals in toxicodynamics or. The available data in humans indicate that daily doses of up to 6,000 mg for around 8 months were not associated with adverse effects; however in line with many other dietary fibres, large bolus intakes of celluloses were occasionally associated with laxation, but there was a lack of dose–response data available.

The Panel considered that in line with the conceptual framework, it would be useful if risk managers had an indicative total exposure (daily consumption value) for microcrystalline, powdered and modified celluloses used as food additives, which would not pose a health risk and uses up to this value would not require a further risk assessment. The Panel considered this could be based on all the reported NOAELs from subchronic and chronic toxicity studies (ranging from 2100 to more than 9000 mg/kg bw/day), human data and allowing for interindividual uncertainty. The Panel considered an indicative total exposure (daily consumption value) of around 660 to 900 mg/kg bw per day for microcrystalline, powdered and modified celluloses.

To assess the dietary exposure to celluloses (E 460–466, E 468 and E 469) from their use as food additives, the combined exposure was calculated based on (1) maximum levels of data provided to EFSA (defined as the *maximum level exposure assessment scenario*) and (2) reported use levels (defined as the *refined exposure assessment scenario brand-loyal* and *non-brand-loyal consumer scenario*).

Celluloses (E 460–466, E 468 and E 469) are authorised in a wide range of foods. The Panel did identify brand loyalty to specific food categories in infants and toddlers (e.g. flavoured drinks). Further, the Panel considered that the non-brand-loyal scenario covering other population groups was appropriate and a realistic scenario for risk characterisation because it was assumed that the population would probably be exposed long-term to the food additive present at the mean reported use in processed food.

A refined estimated exposure assessment scenario taking into account the food for special medical purpose (FSMP) for infants and young children (Food category (FC) 13.1.5.1 dietary foods for infants for special medical purposes and special formulae for infants and 13.1.5.2 dietary foods for babies and young children for special medical purposes as defined by Commission Directive 1999/22/EC in which E 466 is authorised) was also performed to estimate exposure for infants and toddlers who may be on a specific diet. However, no reported use levels were made available by industry for these food categories. Thus, MPLs of E 466 for FSMP were used. The Panel noted that according to Mintel, very few baby foods were on the European market containing E 466. This was in line with the fact that no data were submitted for the food categories 13.1.5.1 and 13.1.5.2.

A refined estimated exposure assessment scenario taking into account the consumption of food supplements for consumers only, were also performed to estimate exposure for children, adolescents, adults and the elderly, as exposure via food supplements may deviate largely from that via food, and the number of food supplements consumers may be low depending on populations and surveys.

The refined estimates were based on 26 out of 84 food categories in which celluloses (E 460–466, E 468 and E 469) are authorised. The Panel considered that the uncertainties identified would, in general, result in an overestimation of the exposure to celluloses (E 460–466, E 468 and E 469) as food additives in European countries for the refined scenario if it is considered that the food additives may not be used in food categories for which no usage data have been provided.

The Panel noted that given the information from the Mintel's Global New Products Database (GNPD), it may be assumed that celluloses (E 460–466, E 468 and E 469) are used in food categories for which no data have been provided by food industry. The main food categories, in terms of amount consumed, not taken into account were processed fermented milk products, cheeses (unripened, processed), fish and fishery products and breakfast cereals. However, according to the Mintel GNPD, in the European Union (EU) market, a small percentage (< 1%) of food products belonging to these food categories are labelled with celluloses (E 460–466, E 468 and E 469). Therefore, the Panel considered that if these uncertainties were confirmed, it would result in a slight underestimation of the exposure.

The Panel further noted that the exposure to celluloses (E 460–466, E 468 and E 469) from their use according the Annex III to Regulation (EC) No 1333/2008 was not considered in the exposure assessment.

The Panel also noted that the refined exposure estimates were based on information provided on the reported levels of use of celluloses (E 460–466, E 468 and E 469). If actual practice changes, this refined estimates may no longer be representative and should be updated.

Following the conceptual framework for the risk assessment of certain food additives re-evaluated under Commission Regulation (EU) No 257/2010 (EFSA ANS Panel, 2014) and given that:

- their structural, physicochemical and biological similarities, allows for read-across between all the celluloses
- animal and human data demonstrate that microcrystalline cellulose (E 460(i)) and powdered cellulose (E 460(ii)) are not absorbed intact in the gastrointestinal tract but could be fermented by intestinal microbiota. Chemically modified celluloses are not absorbed intact, nor fermented, but are excreted intact via the faeces
- using the read-across approach, adequate data on short- and long-term toxicity and carcinogenicity and reproductive toxicity are available,
- despite the limitations of some of the studies, the available data do not indicate a genotoxic concern for microcrystalline cellulose, methyl cellulose and carboxy methyl cellulose, and by read-across, of the other modified and unmodified celluloses
- no adverse effects were reported after repeated doses up to 35 g/person of microcrystalline cellulose or powdered cellulose; oral ingestion of some modified celluloses up to 6,000 mg/person per day for 8 months in patients suffering from diarrhoea or constipation was well tolerated;
- adequate combined exposure data were available; in the general population, the highest 95th percentile refined exposure assessment estimates calculated based on the reported data from food industry was 506 mg/kg bw per day in toddlers (brand-loyal scenario)
- an indicative high refined exposure assessment of up to 448 mg/kg bw per day for the elderly has been calculated at the 95th percentile among the population classes consuming food supplements

The Panel concluded that there was no need for a numerical ADI and that there would be no safety concern at the reported uses and use levels for the unmodified and modified celluloses (E 460(i));

E 460(ii); E 461–466; E 468 and E 469). The Panel further suggested an indicative total exposure (daily consumption value) of 660–900 mg/kg bw per day where these conclusions would remain valid.

Concerning the use of sodium carboxy methyl cellulose (E 466) in 'dietary foods for special medical purposes and special formulae for infants' (FC 13.1.5.1) and in 'dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC' (FC 13.1.5.2), and given that:

- for infants and toddlers consumers only of FSMP, the highest 95th percentile refined exposure estimate was 1,557 mg/kg bw per day in infants;
- no adequate specific studies addressing the safety of use of sodium carboxy methyl cellulose (E 466) in this population under certain medical conditions were available;

the Panel concluded, that the available data did not allow for an adequate assessment of the safety of use of sodium carboxy methyl cellulose (E 466) in infants and young children consuming foods belonging to the categories 13.1.5.1 and 13.1.5.2. The Panel noted that E 466 seemed not to be used in these food categories as no use or use levels were submitted by industry and only very few food belonging to these categories appeared to be labelled with E 466.

The Panel recommended that the European Commission considers lowering the maximum limits for the toxic elements arsenic, lead, mercury and cadmium present as impurities in the EU specifications for unmodified and modified celluloses re-evaluated in the present opinion (E 460(i), E 460(ii), E 461, E 462, E 463, E 464, E 465, E 466, E 468 and E 469) should be revised to ensure that these food additives will not be a significant source of exposure to these toxic elements in food, in particular for infants and children.

Table of contents

1. Introduction

The present opinion deals with the re-evaluation of microcrystalline cellulose (E 460(i)), powdered cellulose (E 460(ii)), methyl cellulose (E 461), ethyl cellulose (E 462), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464), ethyl methyl cellulose (E 465), sodium carboxy methyl cellulose (E 466), cross-linked carboxy methyl cellulose (E 468) and enzymatically hydrolysed carboxy methyl cellulose (E 469) when used as food additives. These celluloses are authorised food additives in the EU according to Annex II and Annex III of Regulation (EC) No 1333/2008.

For the purpose of this opinion, the term modified cellulose is used for all the celluloses mentioned above.

1.1. Background and Terms of Reference as provided by the European Commission

1.1.1. Background

Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives requires that food additives are subject to a safety evaluation by the European Food Safety Authority (EFSA) before they are permitted for use in the European Union. In addition, it is foreseen that food additives must be kept under continuous observation and must be re-evaluated by EFSA.

For this purpose, a programme for the re-evaluation of food additives that were already permitted in the European Union before 20 January 2009 has been set up under the Regulation (EU) No 257/2010[1]. This Regulation also foresees that food additives are re-evaluated whenever necessary in light of changing conditions of use and new scientific information. For efficiency and practical purposes, the re-evaluation should, as far as possible, be conducted by group of food additives according to the main functional class to which they belong.

The order of priorities for the re-evaluation of the currently approved food additives should be set on the basis of the following criteria: the time since the last evaluation of a food additive by the Scientific Committee on Food (SCF) or by EFSA, the availability of new scientific evidence, the extent of use of a food additive in food and the human exposure to the food additive taking also into account the outcome of the Report from the Commission on Dietary Food Additive Intake in the EU of 2001. The report 'Food additives in Europe 2000' submitted by the Nordic Council of Ministers to the Commission, provides additional information for the prioritisation of additives for re-evaluation.

In 2003, the Commission already requested EFSA to start a systematic re-evaluation of authorised food additives. However, as a result of adoption of Regulation (EU) 257/2010 the 2003 Terms of References are replaced by those below.

1.1.2. Terms of Reference

The Commission asks EFSA to re-evaluate the safety of food additives already permitted in the Union before 2009 and to issue scientific opinions on these additives, taking especially into account the priorities, procedures and deadlines that are enshrined in the Regulation (EU) No 257/2010 of 25 March 2010 setting up a programme for the re-evaluation of approved food additives in accordance with the Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives.

1.1.3. Interpretation of Terms of Reference

Specific toxicity data were not always available for all the celluloses for all endpoints. However, given their structural, physicochemical and biological similarities, the Panel considered it possible to read-across between all the celluloses.

The ANS Panel described its risk assessment paradigm in its Guidance for submission for food additive evaluations in 2012 (EFSA ANS Panel, 2012). This Guidance states, that in carrying out its risk assessments, the Panel sought to define a health-based guidance value e.g. an Acceptable Daily Intake (ADI) (IPCS, 2004) applicable to the general population. According to the definition above, the ADI as established for the general population does not apply to infants below 12 weeks of age (JECFA,

[1] Commission Regulation (EU) No 257/2010 of 25 March 2010 setting up a programme for the re-evaluation of approved food additives in accordance with Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives. OJ L 80, 26.3.2010, p. 19–27.

1978; SCF, 1998). In this context, the re-evaluation of the use of sodium carboxy methyl cellulose (E 466) in food for infants below 12 weeks represents a special case for which specific recommendations were given by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (JECFA, 1972, 1978), by the SCF (SCF, 1996, 1998) and by EFSA (EFSA Scientific Committee, 2017). The Panel endorsed these recommendations.

In the current EU legislation (Annex II of Regulation (EC) No 1333/2008[1]), use levels of additives in food for infants under the age of 12 weeks are included in categories 13.1.1 and 13.1.5.1.[2] The Panel considers that these uses would require a specific risk assessment in line with the recommendations given by JECFA and SCF and endorsed by the Panel in its current Guidance for submission for food additives evaluations (EFSA ANS Panel, 2012). Therefore, a risk assessment for the general population is not considered applicable for infants under the age of 12 weeks, and will be performed separately.

This re-evaluation refers exclusively to the uses of celluloses as food additives in food, including food supplements and does not include a safety assessment of other uses of celluloses.

1.2. Information on existing authorisations and evaluations

In 1978, the SCF endorsed the 'ADI not specified' established by JECFA for microcrystalline cellulose and powdered cellulose. The Committee did not give any details of the data considered (SCF, 1978). In 1995, the SCF evaluated the presumed persorption and advised: (1) that microcrystalline cellulose of any particle size should not be used in foods specially prepared for infants and young children and, (2) a particle size > 5 μm should be introduced in the specification (SCF, 1995). In 1999, the SCF assessed the additional toxicological data and confirmed the 'ADI not specified'. As a matter of precaution, the Committee repeated the advice that particle size should not be lower than 5 μm with a tolerance of 10% by the number of particles (SCF, 1999).

In 1976, an 'ADI not specified' was allocated by JECFA for powdered cellulose (JECFA, 1976). The Committee stated that the toxicological evaluation performed for microcrystalline cellulose (JECFA, 1975) should also apply to powdered cellulose (JECFA, 1976). In the latest evaluation (JECFA, 1998a,b, 1999a,b), the Committee concluded that the toxicological data from humans and animals provided no evidence for toxic effects after the ingestion of microcrystalline cellulose in food, and endorsed the previous evaluation 'ADI not specified'. However, the Committee stated that small particles of other materials may be persorbed and that the extent of persorption is greater with sub-micrometer particles. Despite the absence of any demonstrated persorption of microcrystalline cellulose in the recent animal studies, the Committee revised the specifications for microcrystalline cellulose to limit the content of particles less than 5 μm in diameter (see Section 2.2).

Microcrystalline cellulose (E 460(i)) and powdered cellulose (E 460(ii)) were also evaluated by the Nordic Council of Ministers (TemaNord, 2002). The Committee concluded that microcrystalline cellulose and powdered cellulose as defined by the specifications is covered by the toxicological evaluation, including restriction on particle size.

Microcrystalline cellulose (E 460(i)) and powdered cellulose (E 460(ii)) (PM Ref. 43280) are included in the Union list of authorised substances that may be intentionally used in the manufacture of plastic layers in plastic materials and articles (Annex I to Commission Regulation (EU) No 10/2011[3]). Furthermore, microcrystalline cellulose (E 460(i)) is permitted as an antioxidant in cosmetic products (European Commission database-CosIng). Microcrystalline cellulose (E 460(i)) and powdered cellulose (E 460(ii)) are included in the European Union Register of feed additives (Regulation (EC) No 1831/2003[4]).

Methyl cellulose (E 461), ethyl cellulose (E 462), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464), ethyl methyl cellulose (E 465), sodium carboxy methyl cellulose (E 466), cross-linked carboxy methyl cellulose (E 468) and enzymatically hydrolysed carboxy methyl cellulose (E 469) are listed in Commission Regulation (EU) No 231/2012[5] as authorised food additives in the EU

[2] Food of category 13.1.1: Infant formulae as defined by Directive 2006/141/EC; Food of category 13.1.5.1: Dietary foods for infants for special medical purposes and special formulae for infants. This interpretation also applies to those food additives in food category 13.1.5.2 (Dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC) for which exceptional uses in food for infants under the age of 12 weeks are indicated.

[3] Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food. OJ L 12, 15.1.2011, p. 1–89.

[4] Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29.

[5] Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council. OJ L 83, 22.3.2012, p. 1.

and are used as stabilisers, emulsifiers, thickeners, humectants, anticaking agents, foaming agents, bulking agents, gelling agents and glazing agents.

These substances have been previously evaluated by JECFA in 1989 (JECFA, 1990) and 1998 (JECFA, 1999a,b). An 'ADI not specified' was established for each modified cellulose E 461–E 466 and E 469 (JECFA, 1990, 1999a,b).

Toxicological data for methyl cellulose (E 461), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464), methyl ethyl cellulose (E 465) and sodium carboxy methyl cellulose (E 466) were re-evaluated by the SCF in 1992 (SCF, 1994). The Committee allocated an ADI 'not specified' to the five modified celluloses. The other modified celluloses, ethyl cellulose (E 462) and enzymatically hydrolysed sodium carboxy methyl cellulose (E 469) were not evaluated by the SCF.

In 1998, the SCF accepted the use of sodium carboxy methyl cellulose (E 466) in foods for special medical purposes (FSMP) for infants and young children at levels up to 10 g/L in liquid foods and up at 10 g/kg in solid foods. The Committee earlier reserved its opinion on a request to use E 466 in weaning foods pending completion of its work on persorption of macromolecular additives, but noted that otherwise the toxicological data did not indicate any effects likely to be of concern for infants and young children over weaning age. However, the Committee has since been informed that sodium carboxy methyl cellulose in water is in colloidal form and hence is not likely to be persorbed.

Cross-linked sodium carboxy methyl cellulose (E 468) is listed in Commission Regulation (EU) No 231/2012 as an authorised food additive in the EU and has been previously evaluated by JECFA in 2003 (JECFA, 2003). At its 59th meeting, JECFA concluded that the ADI could not be specified (JECFA, 2003).

Cross-linked sodium carboxy methyl cellulose (E 468) is the sodium salt of thermally cross-linked partly O-carboxymethylated cellulose, the use of which is solely as a carrier for sweeteners.

The SCF had accepted the use of cross-linked sodium carboxy methyl cellulose (E 468) on the grounds of lack of toxicity in a limited data set and a history of safe use of the parent compound sodium carboxy methyl cellulose (SCF, 1996, 1998). In 1996, no ADI was established due to insufficient toxicological data, but the use of cross-linked sodium carboxy methyl cellulose was deemed acceptable as a disintegrant for sweetener tablets due to its limited use through this application. The most recent SCF opinion dating from 1998, refers to new data submitted to the Committee, and recommends the use of cross-linked sodium carboxy methyl cellulose (E 468) as a disintegrant at a level not exceeding 30 g/kg in dietary supplements. The Committee's recommendation was based on the newly available technical and toxicological data and the long history of safe use of the parent compound, sodium carboxy methyl cellulose. The parent compound is stated to be poorly absorbed in humans and animals, with a likely further reduction in absorption as a consequence of cross-linking.

Cross-linked sodium carboxy methyl cellulose was thereafter reviewed by JECFA in 2003. The evaluation set a new ADI of 'ADI not specified', describing the substance as 'poorly absorbed' and of 'low toxicity', and with consideration to the available toxicological data which were consistent with that of other modified celluloses.

In 2002, the Nordic Council reviewed cross-linked sodium carboxy methyl cellulose and concluded that there was no need for a re-evaluation (TemaNord, 2002).

Modified celluloses are included in the Union list of authorised substances that may be intentionally used in the manufacture of plastic layers in plastic materials and articles (Annex I to Commission Regulation (EU) No 10/2011) (methyl cellulose (E 461), PM Ref. 66240; ethyl cellulose (E 462), PM Ref. 53280; hydroxypropyl cellulose (E 463), PM Ref. 61680; hydroxypropyl methyl cellulose (E 464), PM Ref. 66700; ethyl methyl cellulose (E 465), PM Ref. 66640; sodium carboxy methyl cellulose (E 466); (hydrolysed) carboxy methyl cellulose (E 469), PM Ref. 42640).

Furthermore, in 2010, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA Panel) issued an opinion addressing the scientific substantiation of health claims in relation to hydroxypropyl methylcellulose (EFSA NDA Panel, 2010a,b). It was concluded that a cause and effect relationship has been established between the consumption of hydroxypropyl methylcellulose and a reduction of post-prandial glycaemic responses, as well as the maintenance of normal blood cholesterol concentrations.

2. Data and methodologies

2.1. Data

The Panel was not provided with a newly submitted dossier. EFSA launched public calls for data,[6,7,8,9] to collect relevant information from interested parties.

The Panel based its assessment on information submitted to EFSA following the public calls for data, information from previous evaluations and additional available literature up to the last Working Group (WG) meeting before the adoption of the opinion. Attempts were made at retrieving relevant original study reports on which previous evaluations or reviews were based, however not always these were available to the Panel.

The EFSA Comprehensive European Food Consumption Database (Comprehensive Database[10]) was used to estimate the dietary exposure.

The Mintel's Global New Products Database (GNPD) is an online database which was used for checking the labelling of products containing E 460(i), E 460(ii), E 461–466, E 468–469 within the EU's food products, as GNPD shows the compulsory ingredient information presented in the labelling of products.

2.2. Methodologies

The assessment was conducted in line with the principles described in the EFSA Guidance on transparency in the scientific aspects of risk assessment (EFSA Scientific Committee, 2009) and following the relevant existing Guidances from the EFSA Scientific Committee.

The ANS Panel assessed the safety of microcrystalline cellulose (E 460(i)), powdered cellulose (E 460(ii)), methyl cellulose (E 461), ethyl cellulose (E 462), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464), ethyl methyl cellulose (E 465), sodium carboxy methyl cellulose (E 466), cross-linked carboxy methyl cellulose (E 468) and enzymatically hydrolysed carboxy methyl cellulose (E 469) as food additives in line with the principles laid down in Regulation (EU) 257/2010 and in the relevant guidance documents: Guidance on submission for food additive evaluations by the Scientific Committee on Food (SCF, 2000) and taking into consideration the Guidance for submission for food additive evaluations in 2012 (EFSA ANS Panel, 2012).

When the test substance was administered in the feed or in the drinking water, but doses were not explicitly reported by the authors as mg/kg bw per day based on actual feed or water consumption, the daily intake was calculated by the Panel using the relevant default values as indicated in the EFSA Scientific Committee (2012) for studies in rodents or, in the case of other animal species, by JECFA (2000a,b,c). When in human studies in adults (aged above 18 years) the dose of the test substance administered was reported in mg/person per day, the dose in mg/kg bw per day was calculated by the Panel using a body weight of 70 kg as default for the adult population as described in the EFSA Scientific Committee Guidance document (EFSA Scientific Committee, 2012).

Dietary exposure of microcrystalline cellulose (E 460(i)), powdered cellulose (E 460(ii)), methyl cellulose (E 461), ethyl cellulose (E 462), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464), ethyl methyl cellulose (E 465), sodium carboxy methyl cellulose (E 466), cross-linked carboxy methyl cellulose (E 468) and enzymatically hydrolysed carboxy methyl cellulose (E 469) from their use as food additives was estimated combining the food consumption data available within the EFSA Comprehensive European Food Consumption Database with the maximum permitted levels (MPLs) and reported use levels submitted to EFSA following a call for data. Different exposure scenarios were calculated. Uncertainties on the exposure assessment were identified and discussed with regard to their impact on the final exposure calculation.

[6] Call for scientific data on food additives permitted in the EU and belonging to the functional classes of emulsifiers, stabilisers and gelling agents. Published: 22 November 2009. Available online: http://www.efsa.europa.eu/en/dataclosed/call/ans091123.

[7] Call for technical data on certain thickening agents permitted as food additives in the EU. Published: 19 December 2014. Available online: http://www.efsa.europa.eu/it/data/call/141219

[8] Call for food additives usage level and/or concentration data in food and beverages intended for human consumption. Published: 12 October 2015. Available online: http://www.efsa.europa.eu/en/data/call/151012

[9] Call for technical data on certain starches and celluloses authorised as food additives in the EU. Published 11 February 2016. http://www.efsa.europa.eu/sites/default/files/consultation/160211.pdf

[10] Available online: http://www.efsa.europa.eu/en/datexfoodcdb/datexfooddb.htm

3. Assessment

3.1. Technical data

3.1.1. Identity of the substances

Cellulose is a linear homopolymer consisting of repeating β-D-glucopyranosyl units linked via (1,4) glycosidic bonds (Figure 1). It is the most abundant substance occurring in nature and an important structural component of the primary cell wall of green plants, many forms of algae and the oomycetes (Iijima and Takeo, 2000; Coffey et al., 2006).

Cellulose has the CAS Registry No 9004-34-6 and the EC (EINECS) Number 232-674-9. The molecular formula is $(C_6H_{10}O_5)_m$; 'm' (degree of polymerisation (DP)) is dependent on the origin of the cellulolytic material. The molecular weight has been calculated to be approximately from 50,000 to 2,500,000, corresponding to (DP) 300–15,000 glucose units. As an example, for native cellulose the DP varies from 3,500 to 10,000 with molecular weights of 600,000–1,500,000 (Hamilton and Mitchell, 1964), although for cotton, the DP could be as high as 15,000 (Holtzapple, 2003). According to Stepan et al., 2016, the cellulose of cotton linter had an average molecular weight of 253,770, which corresponds to a DP of 1,450.

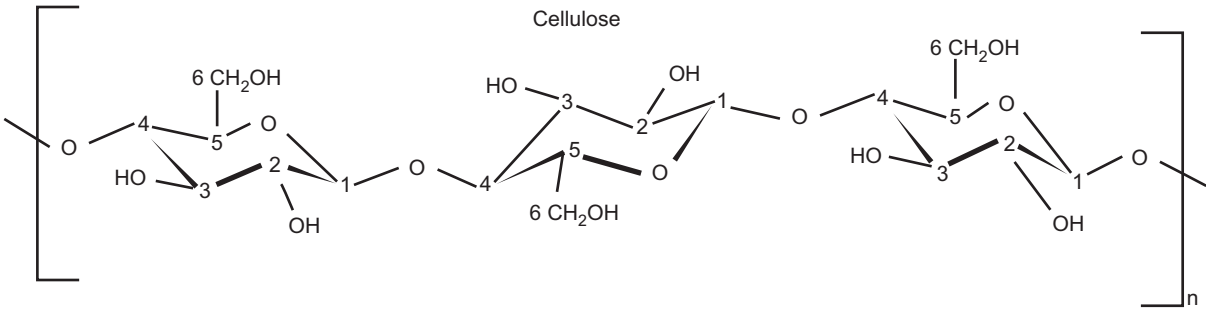


Figure 1: Example of a general formula of a native cellulosic structure ('n' being variable, depending on the origin of the cellulolytic material)

Cellulose is described as a rigid material in which the molecules are associated, over extended regions, forming polycrystalline, fibrous bundles. The crystalline regions are hold together by a large number of hydrogen bonds and are separated and connected by amorphous regions (BeMiller and Whistler, 1996).

Cellulose is insoluble in water because of strong hydrogen bonding in its crystal lattice. However, it is soluble in a number of solvents, including concentrated acids (e.g. 85% phosphoric, 72% sulfuric and 40% hydrochloric acid) and inorganic salt solutions (e.g. cuprammonium hydroxide, cadmium ethylenediamine solvent also known as cadoxen) (Holtzapple, 2003).

Celluloses are subdivided into three classes: α-, β- and γ-cellulose; all have the same chemical structure but differ in their DP: α-cellulose DP > 200; β-cellulose DP 30–200; γ-cellulose DP 10–30 (Chen, 2014).

Celluloses differ in their solubility in 17.5% NaOH: α-cellulose is the fraction that is not removed by treatment with 17.5% NaOH at 20°C; the fraction soluble in 17.5% NaOH contains β-cellulose and γ-cellulose; the subfraction precipitating after acidification of the alkaline liquor is β-cellulose; the acid-base soluble fraction that remains dispersed is γ-cellulose (Walter, 1998).

3.1.1.1. Microcrystalline cellulose (E 460(i))

According to Commission Regulation (EU) No 231/2012, microcrystalline cellulose is purified, partially depolymerised cellulose prepared by treating α-cellulose, obtained as a pulp from strains of fibrous plant material, with mineral acids. The DP is typically < 400; the molecular weight is about 36,000 g/mol.

Microcrystalline cellulose is purified, partially depolymerised cellulose with shorter crystalline polymer chains.

Synonyms: microcrystalline cellulose is known as cellulose gel (JECFA, 2009).

Microcrystalline cellulose is a fine, white, odourless, crystalline powder. The particles are insoluble but able to swell in water, in dilute alkali and acids, and in most organic solvents. The substance is soluble in NaOH solution (Klose and Glicksman, 1990; Coffey et al., 2006). At concentrations below

1%, microcrystalline cellulose forms colloidal solutions, and above 1%, thixotropic gels (Klose and Glicksman, 1990).

3.1.1.2. Powdered cellulose (E 460(ii))

According to the definition of Commission Regulation (EU) No 231/2012, powdered cellulose is purified, mechanically disintegrated cellulose prepared by processing α-cellulose obtained as a pulp from strains of fibrous plant materials. The DP is predominantly ≥ 1,000 and greater, corresponding to a molecular weight of > 160,000 (JECFA, 2006a).

In Commission Regulation (EU) No 231/2012, the substance is described as a white, odourless powder, which is insoluble in water, ethanol, ether and dilute mineral acids, but slightly soluble in sodium hydroxide solution.

Powdered cellulose is able to swell in water, dilute acid and most solvents, while alkali solutions lead to swelling and dissolution of the present hemicelluloses (Coffey et al., 2006).

3.1.1.3. Chemically modified celluloses (E 461–466, E 468 and E 469)

Methyl cellulose (E 461), ethyl cellulose (E 462), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464) and ethyl methyl cellulose (E 465) are celluloses obtained synthetically from fibrous plant material. Each of the celluloses is partially etherified with methyl groups, ethyl groups, hydroxypropyl groups and contains a small degree of hydroxypropyl substitution, and methyl and ethyl groups, respectively (Figure 2).

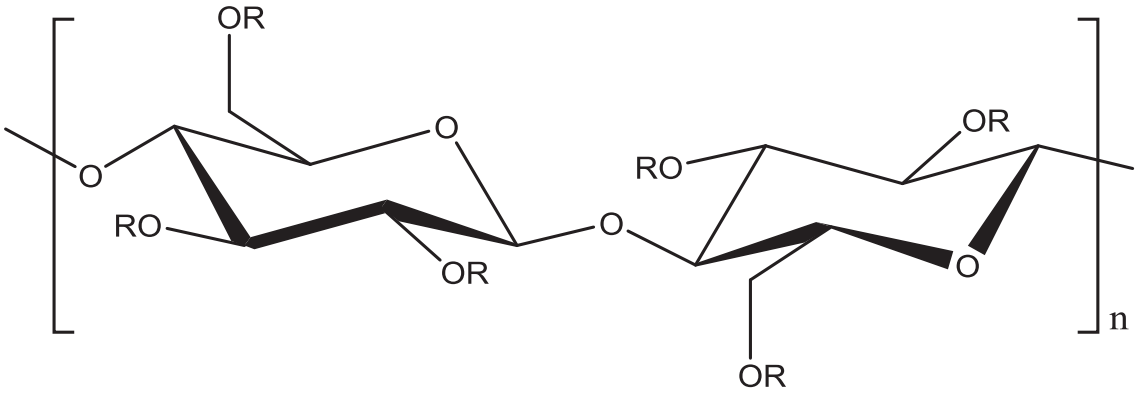
Sodium carboxy methyl cellulose (E 466) is the partial sodium salt of a carboxymethyl ether of cellulose.

Cross-linked sodium carboxy methyl cellulose (E 468) is obtained from carboxy methyl cellulose by acidifying and heating the aqueous suspension.

Enzymatically hydrolysed carboxy methyl cellulose sodium salt (E 469) is obtained from carboxy methyl cellulose by enzymatic digestion with a cellulase produced *by Trichoderma longibrachiatum* (formerly *Trichoderma reesei*).

All modified celluloses are derived from cellulose. They carry the cellulose backbone which consists of a polymer of β-(1→4) linked D-glucopyranose units (also called anhydroglucose unit (AGU)) (Freudenberg and Braun, 1928; Gardner and Blackwell, 1974). The hydroxyl groups at the carbon atoms C-2, C-3 and C-6 of the glucopyranose are more or less completely etherified depending on the used substitution reagent and conditions during manufacturing (Klemm et al., 1998; Murray, 2009; Qi et al., 2009).

The average number of hydroxyl groups substituted per glucopyranose unit is known as degree of substitution (DS). A complete substitution would provide a DS of 3. In the case of hydroxypropyl cellulose (E 463) and hydroxypropyl methyl cellulose (E 464), the DS can be higher than 3 because the hydroxypropyl group added also contains a hydroxyl group which can be etherified (Klemm et al., 1998; Desai et al., 2006).



E461 R= H or $-CH_3$
E462 R= H or $-CH_2CH_3$
E463 R= H or $-CH_2CH(OH)CH_3$ or $-CH_2CH(CH_3)OCH_2CH(OH)CH$
E464 R= H or $-CH_3$ or $-CH_2CH(OH)CH_3$
E465 R= H or $-CH_3$ or $-CH_2CH_3$
E466 R= H or $-CH_2COONa$ or $-CH_2COOH$
E469 R= H or $-CH_2COONa$ or $-CH_2COOH$

Figure 2: General chemical structure of modified celluloses E 461–466 and E 468 and E 469, where R represents hydrogen or specific groups, as indicated. In this structure, 'n' represents the number of anhydrocellobiose repeating units

The CAS Registry Numbers and EINECS numbers of the chemically modified celluloses (E 461–466, E 468 and E 469) are given in Table 1.

Table 1: CAS Registry Numbers and EINECS Numbers of chemically modified celluloses (Wüstenberg, 2015; ChemIdplus)

Substance	CAS registry number	EC (EINECS)[a] number	Molecular formula
Methyl cellulose (E 461)	9004-67-5	618-391-7	$C_6H_7O_2(OH)_x(OCH_3)_y$ x = 1.00–1.55; y = 2.00–1.45; x + y = 3.00 (y = degree of substitution)
Ethyl cellulose (E 462)	9004-57-3	618-384-9	C_2H_6O.x-unspecified
Hydroxypropyl cellulose (E 463)	9004-64-2	618-388-0	$[C_6H_7O_2(OH)_x(OCH_2CHOHCH_3)_y(OCH_2CH[R_w]CH_3)_z]_n$ x + y + z = 3; y + z(1 + w) ≤ 4.6 R: substituent with 'w' hydroxypropyl groups
Hydroxypropyl methyl cellulose (E 464)	9004-65-3	618-389-6	$[C_6H_7O_2(OH)_x(OCH_3)_y(OCH_2CHOHCH_3)_z]_n$ z = 0.07–0.34; y = 1.12–2.03; x = 3 – (z + y), (z + y) = degrees of substitution
Ethyl methyl cellulose (E 465)	9004-59-5[b]	–	$[C_6H_7O_2(OH)_x(OCH_3)_y(OC_2H_5)_z]_n$, z = 0.57–0.8; y = 0.2–0.4; x = 3 – (x + y) (x + y) = degrees of substitution
Sodium carboxy methyl cellulose (E 466)	9004-32-4	618-378-6	$[C_6H_7O_2\ (OH)_x\ (OCH_2COONa)_y]_n$ n ≥ 4 x = 1.50–2.80; y = 0.20–1.50; x + y = 3.0 (x + y) = degree of substitution

Substance	CAS registry number	EC (EINECS)[a] number	Molecular formula
Cross-linked sodium carboxy methyl cellulose (E 468)	74811-65-7	–	Substituted anhydroglucose units with as general formula: $C_6H_7O_2(OR_1)(OR_2)(OR_3)$ where R_1, R_2 and R_3 may be any of the following groups in varying proportions: –H $–CH_2–COONa$ $–CH_2–COOH$ Degree of substitution: 0.60–0.85
Enzymatically hydrolysed carboxy methyl cellulose (E 469)	–	–	$[C_6H_7O_2(OH)_x(OCH_2COONa)_y]$ $n \geq 4$ $x = 1.50–2.80$ $y = 0.2–1.50$ $x + y = 3.0$ $(x+y)$ = degree of substitution

CAS: Chemical Abstract Service; EINECS: European Inventory of Existing Commercial Chemical Substances.
(a): According to the ECHA database (ECHA, 2016), EC numbers with format 6xx-xxx-x have no official status and have no legal significance.
(b): The CAS Registry No 9004-69-7 has also been assigned to ethyl methyl cellulose (E 465).

The CAS Registry numbers and EC (or EINECS) numbers reported in Table 1 were subject to confirmatory steps to minimise the uncertainty of a possible equivocal identification. The Panel considered that modified celluloses are complex structures for which — likewise modified starches (EFSA ANS Panel, 2017a,b) — the CAS registration scheme may unintentionally allow that multiple, possibly erratic, or redundant entries exist for identification of a given substance. However, regardless of the potential uncertainty underlying CAS identifiers, the Panel noted that attributing CAS numbers, which are as reliable as possible to such structures, is probably the 'best' available way for a reasonably accurate identification of the chemicals.

Chemically modified celluloses are white or slightly yellowish, odourless and tasteless powders. However, the physical appearance of the modified celluloses depends on the type of substitution, the DP and the DS (Brandt, 2001; Murray, 2009).

All modified celluloses, except ethyl cellulose (E 462) and cross-linked sodium carboxy methyl cellulose (E 468), are water-soluble polymers. Ethyl cellulose (E 462) is the only modified cellulose not soluble in water but soluble in ethanol. Hydroxypropyl cellulose (E 463) and ethyl methyl cellulose (E 465) are both soluble in water and ethanol (Archer, 1991; Brandt, 2001; Cash and Caputo, 2010). However, the solubility of the modified celluloses is influenced by the DS, e.g. sodium carboxy methyl cellulose (CMC, E 466) with a DS < 0.3 is only soluble in alkali. As the DS approaches 0.7, CMC can is easily be dissolved in water, above a DS of 1, CMC (E 466) is less water soluble (Coffey et al., 2006).

The Panel noted that the data provided by industry indicated that the majority of particles of individual modified celluloses were in the range of 10–100 μm. In addition, based on the known ability of cellulose particles to swell in water, the presence of nanoscale material after ingestion is highly unlikely.

Aqueous solutions of modified celluloses are highly viscous, depending on concentration, temperature, average chain length of the macromolecule (DP), and the presence of salts or other additives (Brandt, 2001; Cash and Caputo, 2010).

The rheological behaviour of a solution at a given concentration and temperature may be Newtonian, pseudoplastic, thixotropic or even gel-forming, depending on the chain length, the substituent distribution, and the nature of the ether group (Coffey et al., 2006). The viscosities of 2% neutral, aqueous solutions of modified celluloses at ambient temperature range from 5 to over 10^5 mPa.s (Brandt, 2001).

Aqueous solutions of methyl cellulose (E 461) and hydroxypropyl methyl cellulose (E 464) are characterised by thermal insolubility. Increases in temperature first lead to a minor decrease in viscosity. When the gelling temperature is reached, there is a sharp increase in viscosity. The viscosity or gel strength remains at a constant value. This gelation is a reversible process. Gel temperature and texture are dependent on the DS and substitution type (Haque and Morris, 1993; Haque et al., 1993; Klemm et al., 1998; Brandt, 2001; Coffey et al., 2006; Murray, 2009; Cash and Caputo, 2010).

The pH of aqueous extracts of E 461, E 463, E 464 and E 465 was found to be between 5 and 8, whereas E 462 was neutral. Due to their sodium content, E 466 and E 469 have slightly elevated pH values (between 5 and 8.5 and 6 and 8.5, respectively).

Infrared (IR) and nuclear magnetic resonance (NMR) spectra are available for all modified celluloses except for E 469 (Desai et al., 2006; Qi et al., 2009). Purity data are given by Nurkeeva et al. (2005).

Cross-linked sodium carboxy methyl cellulose (E 468)

Cross-linked sodium carboxy methyl cellulose (E 468) is an internally linked polymer of carboxy methyl cellulose sodium (E 466). It is defined in Commission Regulation (EU) No 231/2012 as the sodium salt of thermally cross-linked partly O-carboxymethylated cellulose.

Cross-linked sodium carboxy methyl cellulose (E 468) has the CAS Registry Number 748-11-65-7. No EC (EINECS) Number has been attributed to E 468. The molecular formula is $C_6H_7O_2(OR_1)(OR_2)(OR_3)$, with R_1, R_2 and R_3 groups in varying proportion (–H, $–CH_2COONa$, $–CH_2COOH$).

A representative structural formula of cross-linked sodium carboxy methyl cellulose (E 468) is shown in Figure 3.

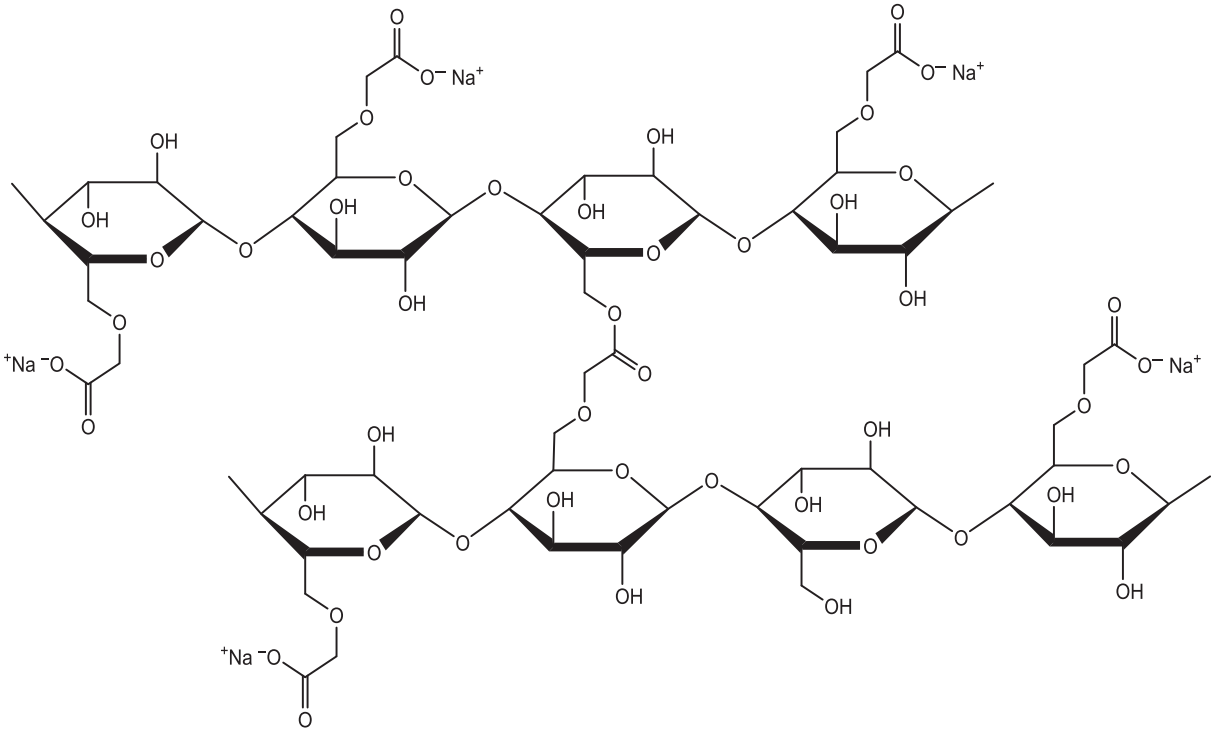


Figure 3: A representative structural formula of cross-linked sodium carboxy methyl cellulose (E 468)

Cross-linked sodium carboxy methyl cellulose is described as a white to off-white, slightly hygroscopic, odourless powder, containing not more than 10% water-soluble matter. The substance is insoluble in ether, alcohol and organic solvents. It is indicated that cross-linking makes the substance fibrous, hydrophilic, highly water-absorbing, which results in pronounced swelling and wicking properties (Mane and Vaidya, 2014).

Common synonyms for chemically modified celluloses are given in Table 2.

Table 2: Synonyms for chemically modified celluloses

Substance	Synonyms
Methyl cellulose (E 461)	Methyl ether of cellulose; Cellulose methyl ether; INS No. 461
Ethyl cellulose (E 462)	Ethyl ether of cellulose; INS No. 462
Hydroxypropyl cellulose (E 463)	Cellulose hydroxypropyl ether; hydroxypropyl ether of cellulose; modified cellulose; INS No. 463
Hydroxypropyl methyl cellulose (E 464)	2-Hydroxypropyl ether of methyl cellulose; INS No. 464; hypromellose (Ph. Eur.)
Ethyl methyl cellulose (E 465)	Ethyl methyl ether of cellulose; methyl ethyl cellulose; MEC; INS No. 465

Substance	Synonyms
Sodium carboxy methyl cellulose (E 466)	Sodium salt of the carboxymethyl ether of cellulose; sodium cellulose glycolate; Na CMC; CMC; cellulose gum; sodium CMC; INS No. 466, carmellose sodium (Ph. Eur.)
Cross-linked sodium carboxy methyl cellulose (E 468)	Cross-linked CMC, cross-linked sodium CMC, cross-linked carboxy methyl cellulose, croscarmellose sodium (Ph. Eur.)
Enzymatically hydrolysed carboxy methyl cellulose sodium (E 469)	Sodium carboxy methyl cellulose; enzymatically hydrolysed; Enzymatically hydrolysed carboxy methyl cellulose; CMC-ENZ; INS No. 469

3.1.2. Specifications

Specifications for microcrystalline cellulose (E 460(i)), powdered cellulose (E 460(ii)), and modified celluloses E 461, E 462, E 463, E 464, E 465, E 466, E 468 and E 469 as defined in Commission Regulation (EU) No 231/2012 and by JECFA are listed in Tables 3–12.

3.1.2.1. Microcrystalline cellulose (E 460(i))

Table 3: Specifications for microcrystalline cellulose (E 460(i)) according to Commission Regulation (EU) No 231/2012 and JECFA (2009)

	Commission Regulation (EU) No 231/2012	JECFA (2009)
Definition	Microcrystalline cellulose is purified, partially depolymerised cellulose prepared by treating α-cellulose, obtained as a pulp from natural strains of fibrous plant material, with mineral acids. The degree of polymerisation is typically less than 400	Purified, partially depolymerised cellulose prepared by treating α-cellulose, obtained as a pulp from fibrous plant material, with mineral acids. The degree of polymerisation is typically less than 400
Assay	Not less than 97% calculated as cellulose on the anhydrous basis	Not less than 97% of carbohydrate calculated as cellulose on the dry basis
Particle size	Not less than 5 μm (not more than 10% of particles of less than 5 μm)	Not more than 10% of the particles have a diameter below 5 μm
Description	A fine white or almost white odourless powder	Fine, white or almost white, odourless, free flowing crystalline powder
Identification		
Solubility	Insoluble in water, ethanol, ether and dilute mineral acids Slightly soluble in sodium hydroxide solution	Insoluble in water, ethanol, ether and dilute mineral acids Slightly soluble in sodium hydroxide solution
Colour reaction	To 1 mg of the sample, add 1 mL of phosphoric acid and heat on a water bath for 30 min. Add 4 mL of a 1 in 4 solution of pyrocatechol in phosphoric acid and heat for 30 min. A red colour is produced	–
Infrared absorption spectroscopy	To be identified	The infrared absorption spectrum of a potassium bromide dispersion of the sample corresponds to the infrared spectrum below
Suspension test	Mix 30 g of the sample with 270 mL of water in a high-speed (12,000 rpm) power blender for 5 min. The resultant mixture will be either a free-following suspension or a heavy, lumpy suspension which flows poorly, if at all, settles only slightly and contains many trapped air bubbles. If a free-flowing suspension is obtained, transfer 100 mL into a 100-mL graduated cylinder and allow to stand for 1 h. The solids settles and a supernatant liquid appears	Mix 30 g of the sample with 270 mL of water in a high-speed (18,000 rpm) blender for 5 min. Transfer 100 mL of the mixture to a 100-mL graduated cylinder, and allow to stand for 3 h. A white, opaque, bubble-free dispersion that forms a supernatant is obtained

	Commission Regulation (EU) No 231/2012	JECFA (2009)
pH	The pH of the supernatant liquid is between 5.0 and 7.5 (10% suspension in water)	5.0–7.5 Shake 5 g of the sample with 40 mL of water for 20 min and centrifuge. Determine the pH of the supernatant
Purity		
Loss on drying	Not more than 7% (105°C, 3 h)	Not more than 7.0% (105°, 3 h)
Water-soluble matter	Not more than 0.24%	Not more than 0.24% Shake 5 g of the sample with approximately 80 mL of water for 10 min, filter through Whatman No. 42 or equivalent filter paper into a tared beaker, wash residue with 20 mL of water and evaporate to dryness on a steam bath. Dry at 105° for 1 h, cool, weigh and calculate as percentage
Sulfated ash	Not more than 0.5% determined at 800 ± 25°C	Not more than 0.05% Test 10 g of the sample (Method I)
Starch	Not detectable To 20 mL of the dispersion obtained in Identification, suspension test, add a few drops of iodine solution and mix. No purplish to blue or blue colour should be produced	Not detectable To 20 mL of the dispersion obtained in the identification test for starch, add a few drops of iodine TS and mix. No purplish to blue or blue colour should be obtained
Carboxyl groups	Not more than 1%	–
Arsenic	Not more than 3 mg/kg	–
Lead	Not more than 2 mg/kg	Not more than 2 mg/kg Determine using an AAS/ICP-AES technique appropriate to the specified level. The selection of sample size and method of sample preparation may be based on principles of methods described in Volume 4 (under 'General Methods, Metallic Impurities')
Mercury	Not more than 1 mg/kg	–
Cadmium	Not more than 1 mg/kg	–

JECFA: Joint FAO/WHO Expert Committee on Food Additives; AAS: atomic absorption spectroscopy; ICP-AES: inductively coupled plasma atomic emission spectroscopy.

In 2017, following a request from the European Commission, the ANS Panel provided a scientific opinion regarding the safety of an amendment of the specifications for microcrystalline cellulose (E 460 (i)) (EFSA ANS Panel, 2017a,b). The applicant proposed an amendment as regards the solubility of the food additive to 'practically insoluble or insoluble in sodium hydroxide solution'. The Panel concluded that the amendment proposed would not give rise to a safety concern. However, the Panel recommended that the concentration of sodium hydroxide solution to be used in the solubility test should be indicated in the EU specifications.

3.1.2.2. Powdered cellulose (E 460(ii))

Table 4: Specifications for powdered cellulose (E 460(ii)) according to Commission Regulation (EU) No 231/2012 and JECFA (2006a)

	Commission Regulation (EU) No 231/2012	**JECFA (2006a)**
Definition	Purified, mechanically disintegrated cellulose prepared by processing α-cellulose obtained as a pulp from natural strains of fibrous plant materials	Purified, mechanically disintegrated cellulose prepared by processing α- cellulose obtained as a pulp from fibrous plant materials; occurs as a white, odourless substance consisting of fibrous particles which may be compressed into self-binding tablets which disintegrate rapidly in water; exists in various grades exhibiting degrees of fineness ranging from a dense free flowing powder to a coarse, fluffy non-flowing material
Assay	Content not less than 92%	Not less than 92% $(C_{12}H_{20}O_{10})_n$
Particle size	Not less than 5 μm (not more than 10% of particles of less than 5 μm)	
Description	A white, odourless powder	–
Identification		
Solubility	Insoluble in water, ethanol, ether and dilute mineral acids. Slightly soluble in sodium hydroxide solution	Insoluble in water, ethanol, ether and dilute mineral acids. Slightly soluble in sodium hydroxide solution
Suspension test	Mix 30 g of the sample with 270 mL of water in a high-speed (12,000 rpm) power blender for 5 min. The resultant mixture will be either a free-flowing suspension or a heavy, lumpy suspension which flows poorly, if at all, settles only slightly and contains many trapped air bubbles. If a free-flowing suspension is obtained, transfer 100 mL into a 100-mL graduated cylinder and allow to stand for 1 h. The solids settle and a supernatant liquid appears	Mix 30 g of the sample with 270 mL of water in a high-speed (12,000 rpm) power blender for 5 min. The resultant mixture will be either a free-flowing suspension or a heavy, lumpy suspension which flows poorly, if at all, settles only slightly and contains many trapped air bubbles. If a free flowing suspension is obtained, transfer 100 mL into a 100-mL graduated cylinder and allow to stand for 1 h. The solids settle and a supernatant liquid appears
pH	The pH of the supernatant liquid is between 5.0 and 7.5 (10% suspension in water)	5.0–7.5 Mix 10 g of the dried sample, accurately weighed, with 90 mL water and allow to stand with occasional stirring for 1 h
Purity		
Loss on drying	Not more than 7% (105°C, 3 h)	Not more than 7% after drying (105°C, 3 h)
Water-soluble matter	Not more than 1.0%	Not more than 1.5% Mix about 6 g of the sample, previously dried, with 90 mL of recently boiled and cooled water and allow to stand with occasional stirring for 10 min. Filter, discard the first 10 mL of filtrate and pass the filtrate through the same filter a second time if necessary to obtain a clear filtrate. Evaporate a 15 mL portion of the filtrate to dryness in a tared evaporation dish on a steam bath, dry at 105° for 1 h. Not more than 15 mg of residue is obtained
Sulfated ash	Not more than 0.3% (800 ± 25°C)	Not more than 0.3% (at approximately 800°C to constant weight)
Starch	Not detectable To 20 mL of the dispersion obtained in Identification, suspension test, add a few drops of iodine solution and mix. No purplish to blue or blue colour should be produced	Not detectable To 20 mL of the mixture obtained in the Identification Test B add a few drops of iodine TS and mix. No purplish-to-blue or blue colour is produced

	Commission Regulation (EU) No 231/2012	JECFA (2006a)
Arsenic	Not more than 3 mg/kg	–
Lead	Not more than 2 mg/kg	Not more than 2 mg/kg Determine using an atomic absorption technique appropriate to the specified level. The selection of sample size and method of sample preparation may be based on the principles of the method described in Volume 4, 'Instrumental Methods'
Mercury	Not more than 1 mg/kg	–
Cadmium	Not more than 1 mg/kg	–

The Panel noted that, according to the EU specifications for microcrystalline cellulose (E 460(i)) and powdered cellulose (E 460(ii)), impurities of the toxic elements arsenic, cadmium, lead and mercury are accepted up concentrations of 3, 1, 2 and 1 mg/kg, respectively. Contamination at those levels could have a significant impact on the exposure to these metals, for which the intake is already close to the health-based guidance values established by EFSA (EFSA, 2009a,b; EFSA CONTAM Panel, 2009, 2010, 2012).

The Panel noted that there are monographs in the European Pharmacopoeia (Ph. Eur. 8th edition, 2014) on 'microcrystalline cellulose' and 'powdered cellulose'. In these monographs, limits for total anaerobic microbial count (TAMC) and total combined yeast and mould count (TYMC) are defined and absence of *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Salmonella* is required.

3.1.2.3. Methyl cellulose (E 461)

Table 5: Specifications for methyl cellulose (E 461) according to Commission Regulation (EU) No 231/2012 and JECFA (2006a)

	Commission Regulation (EU) No 231/2012	JECFA (2006a)
Definition	Methyl cellulose is cellulose obtained directly from strains of fibrous plant material and partially etherified with methyl groups	The methyl ether of cellulose, prepared from wood pulp or cotton by treatment with alkali and methylation of the alkali cellulose with methyl chloride. The article of commerce can be specified further by viscosity
Assay	Content not less than 25% and not more than 33% of methoxyl groups ($-OCH_3$) and not more than 5% of hydroxyethoxyl groups ($-OCH_2CH_2OH$)	Not less than 25% and not more than 33% of methoxyl groups. (Some products of commerce designated 'methyl cellulose' also contain components substituted with small amounts (max. 5%) of hydroxyethyl and/or hydroxypropyl groups. Development of separate specifications for these products should be considered)
Description	Slightly hygroscopic white or slightly yellowish or greyish odourless and tasteless, granular or fibrous powder	Hygroscopic white or off-white, odourless fine granules, filaments or powder
Identification		
Solubility	Swelling in water, producing a clear to opalescent, viscous, colloidal solution Insoluble in ethanol, ether and chloroform Soluble in glacial acetic acid	Swelling in water, producing a clear to opalescent, viscous, colloidal solution; insoluble in ethanol, ether and chloroform. Soluble in glacial acetic acid
Foam test	–	A 0.1% solution of the sample is shaken vigorously. A layer of foam appears. (This test permits the distinction of sodium carboxy methyl cellulose from other cellulose ethers)

	Commission Regulation (EU) No 231/2012	JECFA (2006a)
Precipitate formation	–	To 5 mL of a 0.5% solution of the sample, add 5 mL of a 5% solution of copper sulfate or of aluminium sulfate. No precipitate appears. (This test permits the distinction of sodium carboxy methyl cellulose from other cellulose ethers)
Purity		
Loss on drying	Not more than 10% (105°C, 3 h)	Not more than 10% (105°C, 3 h)
Sulfated ash	Not more than 1.5% (800 ± 25°C)	Not more than 1.5%
pH	Not less than 5.0 and not more than 8.0 (1% colloidal solution)	5.0–8.0 (1 in 100 solution)
Arsenic	Not more than 3 mg/kg	–
Lead	Not more than 2 mg/kg	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg	–
Cadmium	Not more than 1 mg/kg	–

The Panel noted that in JECFA (2006a), descriptions are included for tests on determination of lead and determination of methoxyl groups. The Panel also noted that methyl cellulose specifications include methyl hydroxyethyl cellulose (MHEC) (up to 5% hydroxyethyl substitution is permitted).

3.1.2.4. Ethyl cellulose (E 462)

Table 6: Specifications for ethyl cellulose (E 462) according to Commission Regulation (EU) No 231/2012 and JECFA (2012)

	Commission Regulation (EU) No 231/2012	JECFA (2012)
Definition	Ethyl cellulose is cellulose obtained directly fibrous plant material and partially etherified with ethyl groups	Ethyl ether of cellulose, prepared from wood pulp or cotton by treatment with alkali and ethylation of the alkali cellulose with ethyl chloride. The article of commerce can be specified further by viscosity. Antioxidants permitted for use in food may be added for stabilisation purposes
Assay	Content not less than 44% and not more than 50% of ethoxyl groups ($-OC_2H_5$) on the dried basis (equivalent to not more than 2.6 ethoxyl groups per anhydroglucose unit)	Not less than 44% and not more than 50% of ethoxyl groups ($-OC_2H_5$) on the dried basis (equivalent to not more than 2.6 ethoxyl groups per anhydroglucose unit)
Description	Slightly hygroscopic white to off-white, odourless and tasteless powder	Free flowing, white to light tan powder
Identification		
Solubility	Practically insoluble in water, in glycerol and in propane-1,2-diol but soluble in varying proportions in certain organic solvents depending upon the ethoxyl content. Ethyl cellulose containing less than 46–48% of ethoxyl groups is freely soluble in tetrahydrofuran, in methyl acetate, in chloroform and in aromatic hydrocarbon ethanol mixtures. Ethyl cellulose containing 46–48% or more of ethoxyl groups is freely soluble in ethanol, in methanol, in toluene, in chloroform and in ethyl acetate	Practically insoluble in water, in glycerol, and in propane-1,2-diol, but soluble in varying proportions in certain organic solvents, depending upon the ethoxyl content. Ethyl cellulose containing less than 46–48% of ethoxyl groups is freely soluble in tetrahydrofuran, methyl acetate and aromatic hydrocarbon ethanol mixtures. Ethyl cellulose containing 46–48% or more of ethoxyl groups is freely soluble in ethanol, methanol, toluene and ethyl acetate

	Commission Regulation (EU) No 231/2012	JECFA (2012)
Film forming test	Dissolve 5 g of the sample in 95 g of an 80:20 (w/w) mixture of toluene ethanol. A clear, stable, slightly yellow solution is formed. Pour a few mL of the solution onto a glass plate and allow the solvent to evaporate. A thick, tough, continuous, clear film remains. The film is flammable	Dissolve 5 g of the sample in 95 g of an 80:20 (w/w) mixture of toluene-ethanol. A clear, stable, slightly yellow solution is formed. Pour a few mL of the solution onto a glass plate, and allow the solvent to evaporate. A thick, tough continuous, clear film remains. The film is flammable.
Purity		
Loss on drying	Not more than 3% (105°C, 2 h)	Not more than 3% (105°C, 2 h)
Sulfated ash	Not more than 0.4%	Not more than 0.4%
pH	Neutral to litmus (1% colloidal solution)	Neutral to litmus (1 in 20 suspension)
Arsenic	Not more than 3 mg/kg	–
Lead	Not more than 2 mg/kg	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg	–
Cadmium	Not more than 1 mg/kg	–

The Panel noted that in JECFA (2012) descriptions are included for tests on determination of lead and determination of the ethoxyl content. Furthermore, the Panel noted that in the European Pharmacopeia the concentration of acetaldehyde is limited to 100 ppm (Ph. Eur. 8th edition, 2014).

3.1.2.5. Hydroxypropyl cellulose (E 463)

Table 7: Specifications for hydroxypropyl cellulose (E 463) according to Commission Regulation (EU) No 231/2012 and JECFA (2006b)

	Commission Regulation (EU) No 231/2012	JECFA (2006b)
Definition	Hydroxypropyl cellulose is cellulose obtained directly from strains of fibrous plant material and partially etherified with hydroxypropyl groups	An ether of cellulose containing hydroxypropyl substitution prepared from cellulose by treatment with alkali and propylene oxide. The article of commerce can be specified further by viscosity
Assay	Content not more than 80.5% of hydroxypropoxyl groups ($-OCH_2CHOHCH_3$) equivalent to not more than 4,6 hydroxypropyl groups per anhydroglucose unit on the anhydrous basis	Not more than 80.5% of hydroxypropoxy groups equivalent to not more than 4.6 hydroxypropyl groups per anhydroglucose unit on the dried basis
Description	Slightly hygroscopic white or slightly yellowish or greyish odourless and tasteless, granular or fibrous powder	Slightly hygroscopic, white or off-white, almost odourless, granular or fibrous powder
Identification		
Solubility	Swelling in water, producing a clear to opalescent, viscous, colloidal solution. Soluble in ethanol. Insoluble in ether	Swells in water, producing a clear to opalescent, viscous colloidal solution; insoluble in ethanol; insoluble in ether
Gas chromatography	Determine the substituents by gas chromatography	
Foam formation	–	A 0.1% solution of the sample is shaken vigorously. A layer of foam appears. This test permits the distinction of sodium carboxy methyl cellulose from other cellulose ethers

	Commission Regulation (EU) No 231/2012	JECFA (2006b)
Precipitate formation	–	To 5 mL of a 0.5% solution of the sample, add 5 mL of a 5% solution of copper sulfate or of aluminium sulfate. No precipitate appears. This test permits the distinction of sodium carboxy methyl cellulose from other cellulose ethers
Purity		
Loss on drying	Not more than 10% (105°C, 3 h)	Not more than 10% (105°C to constant weight)
Sulfated ash	Not more than 0.5% (800 ± 25°C)	Not more than 0.5%. Test 1 g of the sample
pH	Not less than 5.0 and not more than 8.0 (1% colloidal solution)	Not less than 5.0 and not more than 8.0 (1 in 100 solution)
Propylene chlorohydrins	Not more than 0.1 mg/kg	Not more than 0.1 mg/kg
Arsenic	Not more than 3 mg/kg	–
Lead	Not more than 2 mg/kg	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg	–
Cadmium	Not more than 1 mg/kg	–

The Panel noted that JECFA and EU specifications state different solubility properties for hydroxypropyl cellulose (E 463) in ethanol (soluble according to Commission Regulation, insoluble according to JECFA.

3.1.2.6. Hydroxypropyl methyl cellulose (E 464)

Table 8: Specifications for hydroxypropyl methyl cellulose (E 464) according to Commission Regulation (EU) No 231/2012 and JECFA (2011a)

	Commission Regulation (EU) No 231/2012	JECFA (2011a)
Definition	Hydroxypropyl methyl cellulose is cellulose obtained directly from strains of fibrous plant material and partially etherified with methyl groups and containing a small degree of hydroxypropyl substitution	Hydroxypropylmethyl cellulose is a methyl cellulose modified by treatment with alkali and propylene oxide by which a small number of 2-hydroxypropyl groups are attached through ether links to the anhydroglucose units of the cellulose. The article in commerce may be further specified by viscosity
Assay	Content not less than 19% and not more than 30% methoxyl groups ($-OCH_3$) and not less than 3% and not more than 12% hydroxypropoxyl groups ($-OCH_2CHOHCH_3$), on the anhydrous basis	Not less than 19% and not more than 30% of methoxy groups ($-OCH_3$) and not less than 3% and not more than 12% hydroxypropoxy groups ($-OCH_2CHOHCH_3$), on the dried basis
Description	Slightly hygroscopic white or slightly yellowish or greyish odourless and tasteless, granular or fibrous powder	Hygroscopic white or off-white powder, or granules or fine fibres
Identification		
Solubility	Swelling in water, producing a clear to opalescent, viscous, colloidal solution. Insoluble in ethanol	Swells in water, producing a clear to opalescent, viscous colloidal solution; insoluble in ethanol
Gas chromatography	Determine the substituents by gas chromatography	–
Foam formation	–	A 0.1% solution of the sample is shaken vigorously. A layer of foam appears. This test permits the distinction of sodium carboxy methyl cellulose from other cellulose ethers

	Commission Regulation (EU) No 231/2012	JECFA (2011a)
Precipitate formation	–	To 5 mL of a 0.5% solution of the sample, add 5 mL of a 5% solution of copper sulfate or of aluminium sulfate. No precipitate appears. This test permits the distinction of sodium carboxy methyl cellulose from other cellulose ethers
Purity		
Loss on drying	Not more than 10% (105°C, 3 h)	Not more than 10% (105°C to constant weight)
Sulfated ash	Not more than 1.5% for products with viscosities of 50 mPa.s or above Not more than 3% for products with viscosities below 50 mPa.s	Not more than 1.5% for products with viscosities of 50 centipoise or above, and not more than 3% for products with viscosities below 50 centipoise
pH	–	Not less than 5.0 and not more than 8.0 (1 in 100 solution)
Propylene chlorohydrins	Not more than 0.1 mg/kg	Not more than 1 mg/kg
Arsenic	Not more than 3 mg/kg	–
Lead	Not more than 2 mg/kg	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg	–
Cadmium	Not more than 1 mg/kg	–

3.1.2.7. Ethyl methyl cellulose (E 465)

Table 9: Specifications for ethyl methyl cellulose (E 465) according to Commission Regulation (EU) No 231/2012 and JECFA (2006c)

	Commission Regulation (EU) No 231/2012	JECFA (2006c)
Definition	Ethyl methyl cellulose is cellulose obtained directly from strains of fibrous plant material and partially etherified with methyl and ethyl groups	A mixed ether of cellulose, prepared from cellulose by treatment with alkali, dimethyl sulfate and ethyl chloride; both the methyl and ethyl groups are attached to the anhydroglucose units by ether linkages. The article of commerce can be specified further by viscosity
Assay	Content on the anhydrous basis not less than 3.5% and not more than 6.5% of methoxyl groups ($-OCH_3$) and not less than 14.5% and not more than 19% of ethoxyl groups ($-OCH_2CH_3$), and not less than 13.2% and not more than 19.6% of total alkoxyl groups, calculated as methoxyl	Methyl ethyl cellulose contains, on the dried basis, not less than 3.5% and not more than 6.5% of methoxyl groups ($-OCH_3$), not less than 14.5% and not more than 19.0% of ethoxyl groups ($-OCH_2CH_3$), and not less than 13.2% and not more than 19.6% of total alkoxyl groups, calculated as methoxyl (on the dry basis)
Description	Slightly hygroscopic white or slightly yellowish or greyish odourless and tasteless, granular or fibrous powder	Hygroscopic and slightly yellowish odourless fibre or powder
Identification		
Solubility	Swelling in water, producing a clear to opalescent, viscous, colloidal solution. Soluble in ethanol. Insoluble in ether	Swelling in water, producing a clear to opalescent, viscous, colloidal solution; insoluble in ethanol
Foam test	–	A 0.1% solution of the sample is shaken vigorously. A layer of foam appears. (This test permits the distinction of sodium carboxy methyl cellulose from other cellulose ether and alginates and natural gums)

	Commission Regulation (EU) No 231/2012	JECFA (2006c)
Precipitate formation	–	To 5 mL of a 0.5% solution of the sample add 5 mL of a 5% solution of copper sulfate or of aluminium sulfate. No precipitate appears. (This test permits the distinction of cellulose ethers from sodium carboxy methyl cellulose, gelatine, carob bean gum and tragacanth gum)
Substituents	–	Determine the substituents by gas chromatography
Purity		
Loss on drying	Not more than 15% for the fibrous form, and not more than 10% for the powdered form (105°C to constant weight)	Not more than 15% for the fibrous form, and not more than 10% for the powdered form, after drying to constant weight
Sulfated ash	Not more than 0.6%	Not more than 0.6%
pH	Not less than 5.0 and not more than 8.0 (1% colloidal solution)	
Arsenic	Not more than 3 mg/kg	–
Lead	Not more than 2 mg/kg	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg	–
Cadmium	Not more than 1 mg/kg	–

The Panel noted that JECFA and EU specifications state different solubility properties for E 465 in ethanol (soluble according to Commission Regulation, insoluble according to JECFA).

3.1.2.8. Sodium carboxy methyl cellulose (E 466)

Table 10: Specifications for sodium carboxy methyl cellulose (E 466) according to Commission Regulation (EU) No 231/2012 and JECFA (2011b)

	Commission Regulation (EU) No 231/2012	JECFA (2011b)
Definition	carboxy methyl cellulose is the partial sodium salt of a carboxymethyl ether of cellulose, the cellulose being obtained directly from strains of fibrous plant material	Prepared from cellulose by treatment with alkali and monochloro-acetic acid or its sodium salt. The article of commerce can be specified further by viscosity
Assay	Content on the anhydrous basis not less than 99.5%	Not less than 99.5% of sodium carboxy methyl cellulose, calculated on the dried basis
Description	Slightly hygroscopic white or slightly yellowish or greyish odourless and tasteless, granular or fibrous powder	White or slightly yellowish, almost odourless hygroscopic granules, powder or fine fibres
Identification		
Solubility	Yields a viscous colloidal solution with water. Insoluble in ethanol	Yield viscous colloidal solution with water; insoluble in ethanol
Foam test	A 0.1% solution of the sample is shaken vigorously. No layer of foam appears. (This test permits the distinction of sodium carboxy methyl cellulose from other cellulose ethers)	Vigorously shake a 0.1% solution of the sample. No layer of foam appears. This test distinguishes sodium carboxy methyl cellulose from other cellulose ethers and from alginates and natural gums
Precipitate formation	To 5 mL of a 0.5% solution of the sample, add 5 mL of 5% solution of copper sulfate or of aluminium sulfate. A precipitate appears. (This test permits the distinction of sodium carboxy methyl cellulose from other cellulose ethers and from gelatine, locust bean gum and tragacanth)	To 5 mL of a 0.5% solution of the sample add 5 mL of a 5% solution of copper sulfate or of aluminium sulfate. A precipitate appears. (This test permits the distinction of sodium carboxy methyl cellulose from other cellulose ethers, and from gelatine, carob bean gum and tragacanth gum)

	Commission Regulation (EU) No 231/2012	JECFA (2011b)
Colour reaction	Add 0.5 g powdered carboxy methyl cellulose sodium to 50 mL of water, while stirring to produce a uniform dispersion. Continue the stirring until a clear solution is produced, and use the solution for the following test: To 1 mg of the sample, diluted with an equal volume of water, in a small test tube, add 5 drops of 1-naphthol solution. Incline the test tube, and carefully introduce down the side of the tube 2 mL of sulfuric acid so that it forms a lower layer. A red-purple colour develops at the interface	Add 0.5 g of powdered carboxy methyl cellulose sodium to 50 mL of water, while stirring to produce a uniform dispersion. Continue the stirring until a clear solution is produced. To 1 mL of the solution, diluted with an equal volume of water, in a small test tube, add 5 drops of 1-naphthol TS. Incline the test tube, and carefully introduce down the side of the tube 2 mL of sulfuric acid so that it forms a lower layer. A red-purple colour develops at the interface
Purity		
Degree of substitution	Not less than 0.2 and not more than 1.5 carboxymethyl groups (–CH_2COOH) per anhydroglucose unit	Not less than 0.20 and not more than 1.50
Loss on drying	Not more than 12% (105°C to constant weight)	Not more than 12% after drying (105°, to constant weight)
pH	Not less than 5.0 and not more than 8.5 (1% colloidal solution)	6.0–8.5 (1 in 100 solution)
Arsenic	Not more than 3 mg/kg	–
Lead	Not more than 2 mg/kg	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg	–
Cadmium	Not more than 1 mg/kg	–
Total glycolate	Not more than 0.4%, calculated as sodium glycolate on the anhydrous basis	Not more than 0.4% calculated as sodium glycolate on the dried basis
Sodium	Not more than 12.4% on the anhydrous basis	Not more than 12.4% on the dried basis
Sodium chloride	–	Not more than 0.5% on the dried basis

The European Pharmacopoeia distinguishes two monographs of sodium carboxy methyl cellulose: Carmellose sodium (Ph. Eur. 8th edition, 3rd supplement 2015), with a sodium content of not less than 6.5% and not more than 10.8% on the anhydrous basis; carmellose sodium, low-substituted (Ph. Eur. 8th edition, 2014), with a sodium content of not less than 2% and not more than 4.5% on the anhydrous basis. Both monographs differ in their criteria for sulfated ash, which are not included in Commission Regulation (EU) No 231/2012 and in the JECFA specifications.

3.1.2.9. Cross-linked sodium carboxy methyl cellulose (E 468)

Table 11: Specifications for cross-linked sodium carboxy methyl cellulose (E 468) according to Commission Regulation (EU) No 231/2012 and JECFA (2006a–g)

	Commission Regulation (EU) No 231/2012	JECFA (2006a–g)
Assay		
Description	Slightly hygroscopic, white to off white, odourless powder	A slightly hygroscopic, white to greyish-white, odourless powder
Identification		
Precipitate formation	Shake 1 g with 100 mL of a solution containing 4 mg/kg methylene blue and allow to settle. The substance to be examined absorbs the methylene blue and settles as a blue, fibrous mass	Mix 1 g of the powdered sample with 100 mL of solution containing 4 mg/kg of methylene blue in water and allow to settle. The substance absorbs methylene blue and settles as a blue, fibrous mass

	Commission Regulation (EU) No 231/2012	JECFA (2006a–g)
Colour reaction	Shake 1 g with 50 mL of water. Transfer 1 mL of the mixture to a test tube, add 1 mL water and 0.05 mL of freshly prepared 40 g/l solution of α-naphthol in methanol. Incline the test tube and add carefully 2 mL of sulfuric acid down the side so that it forms a lower layer. A reddish-violet colour develops at the interface	Add 1 g of the powdered sample to 50 mL water, while stirring to produce a uniform dispersion. Dilute 1 mL of this mixture with 1 mL of water in a small test tube and add 5 drops of 1-naphthol TS. Incline the test tube, and carefully introduce down the side of the tube 2 mL of sulfuric acid so that it forms a lower layer. A red-purple colour develops at the interface
Test for sodium	Passes test	–
pH	Not less than 5.0 and more than 7.0 (1% solution)	Not less than 5.0 and not more than 7.0 (1 in 100 suspension in water)
Solubility	–	Practically insoluble in acetone, in ethanol and in toluene
Purity		
Loss on drying	Not more than 6% (105°C, 3 h)	Not more than 6% (105°C, 3 h)
Water soluble matter	Not more than 10%	Not more than 10%
Degree of substitution	Not less than 0.2 and not more than 1.5 carboxymethyl groups per anhydroglucose unit	Not less than 0.2 and not more than 1.5 carboxymethyl groups ($-CH_2COOH$) per anhydroglucose unit on the dried basis.
Sodium content	Not more than 12.4% on anhydrous basis	–
Arsenic	Not more than 3 mg/kg	–
Lead	Not more than 2 mg/kg	Not more than 2 mg/kg
Cadmium	Not more than 1 mg/kg	–
Mercury	Not more than 1 mg/kg	–
Sulfated ash	–	Not less than 14.0% and not more than 28.0% on the dried basis (2 g of sample)
Sodium chloride and sodium glycolate	–	Not more than 0.5% (sum of sodium chloride and sodium glycolate) on the dried basis

JECFA and the European Pharmacopoeia (Ph. Eur. 8th edition, 2014) include criteria for solubility, sulfated ash and the combined content of sodium chloride and sodium glycolate, which are not included in Commission Regulation (EU) No 231/2012. In addition, the European Pharmacopoeia defines limits for TAMC and TYMC, and requires the absence of *E. coli*.

3.1.2.10. Enzymatically hydrolysed carboxy methyl cellulose (E 469)

Table 12: Specifications for enzymatically hydrolysed carboxy methyl cellulose (E 469) according to Commission Regulation (EU) No 231/2012 and JECFA (2006d)

	Commission Regulation (EU) No 231/2012	JECFA (2006d)
Definition	Enzymatically hydrolysed carboxy methyl cellulose is obtained from carboxy methyl cellulose by enzymatic digestion with a cellulase produced by *Trichoderma longibrachiatum* (formerly *T. reesei*)	The product is the sodium salt of a carboxymethyl ether of cellulose, which has been partially hydrolysed by enzymatic treatment with food-grade *Trichoderma reesei* cellulase. The total content of mono- and disaccharides does not exceed about 7.5%
Assay	Not less than 99.5%, including mono- and disaccharides, on the dried basis	Not less than 99.5%, including mono- and disaccharides, on the dried basis

	Commission Regulation (EU) No 231/2012	JECFA (2006d)
Description	White or slightly yellowish or greyish, odourless, slightly hygroscopic granular or fibrous powder	White or slightly yellowish or greyish, odourless, slightly hygroscopic granular or fibrous powder
Identification		
Solubility	Soluble in water, insoluble in ethanol	Soluble in water; insoluble in ethanol
Foam test	Vigorously shake a 0.1% solution of the sample. No layer of foam appears. This test distinguishes sodium carboxy methyl cellulose, whether hydrolysed or not, from other cellulose ethers and from alginates and natural gums	Vigorously shake a 0.1% solution of the sample. No layer of foam appears. This test distinguishes sodium carboxy methyl cellulose, whether hydrolysed or not, from other cellulose ethers and from alginates and natural gums.
Precipitate formation	To 5 mL of a 0.5% solution of the sample add 5 mL of a 5% solution of copper or aluminium sulfate. A precipitate appears. This test distinguishes sodium carboxy methyl cellulose, whether hydrolysed or not, from other cellulose ethers and from gelatine, carob bean gum and tragacanth gum	To 5 mL of a 0.5% solution of the sample add 5 mL of a 5% solution of copper or aluminium sulfate. A precipitate appears. This test distinguishes sodium carboxy methyl cellulose, whether hydrolysed or not, from other cellulose ethers, and from gelatine, carob bean gum and tragacanth gum
Colour reaction	Add 0.5 g of the powdered sample to 50 mL of water, while stirring to produce a uniform dispersion. Continue the stirring until a clear solution is produced. Dilute 1 mL of the solution with 1 mL of water in a small test tube. Add 5 drops of 1–naphthol TS. Incline the tube, and carefully introduce down the side of the tube 2 mL of sulfuric acid so that it forms a lower layer. A red-purple colour develops at the interface	Add 0.5 g of the powdered sample to 50 mL of water, while stirring to produce a uniform dispersion. Continue the stirring until a clear solution is produced. Dilute 1 mL of the solution with 1 mL of water in a small test tube. Add 5 drops of 1–naphthol TS. Incline the tube, and carefully introduce down the side of the tube 2 mL of sulfuric acid so that it forms a lower layer. A red-purple colour develops at the interface
Viscosity (60% solids)	Not less than 2,500 kg $m^{-1}s^{-1}$ at 25 °C corresponding to an average molecule weight of 5,000 Da	Not less than 2,500 mPa.s corresponding to an average molecular weight of 5,000 Da. This test also distinguishes enzymatically hydrolysed CMC from non-hydrolysed CMC since it is not possible to make a 60% solution of ordinary CMC
Purity		
Degree of substitution	Not less than 0.2 and not more than 1.5 carboxymethyl groups per anhydroglucose unit on the dried basis	Not less than 0.2 and not more than 1.50 carboxymethyl groups (CH_2COOH) per anhydroglucose unit on the dried basis
Loss on drying	Not more than 12% (105°C to constant weight)	Not more than 12% (105°C to constant weight)
pH	Not less than 6.0 and not more than 8.5 (1% colloidal solution)	Not less than 6.0 and not more than 8.5 (1 in 100 solution)
Lead	Not more than 2 mg/kg	Not more than 2 mg/kg
Sodium chloride and sodium glycolate	Not more than 0.5% singly or in combination	Not more than 0.5%, singly or in combination
Residual enzyme activity	Passes test. No change in viscosity of test solution occurs, which indicates hydrolysis of the sodium carboxy methyl cellulose	Passes test

The Panel noted that the content of the tables is not consistent in that heavy metals are not consistently listed at the end of the tables.

3.1.3. Manufacturing process

The raw materials for the production of the different types of celluloses are mainly wood chips. Chemical wood pulping involves the extraction of cellulose from wood by dissolving the lignin that binds the cellulose fibres together. Several processes used in chemical pulping have been described, among these, 'kraft pulping' and 'sulfite pulping' being the most important. The choice of a pulping process is determined by the desired product, the wood species available, and by economic considerations.

In 'kraft pulping' wood chips are digested at elevated temperature and pressure in 'white liquor', being an aqueous solution of sodium sulfide (Na_2S) and sodium hydroxide (NaOH). During digestion the lignin fraction is dissolved. When cooking is complete, the content of the digester is transferred to an atmospheric tank where the spent cooking liquor is separated from the pulp. The pulp then proceeds through various stages of washing, and possibly bleaching, after which it is pressed and dried into the finished product (wood pulp).

In 'sulfite pulping' wood chips are digested under high pressure in the presence of sulfurous acid. To buffer the cooking solution, either sodium bisulfite ($NaHSO_3$), magnesium bisulfite ($Mg(HSO_3)_2$), calcium bisulfite ($Ca(HSO_3)_2$) or ammonium bisulfite ($(NH_4)HSO_3$) is used. Afterwards, the pulp is treated in a similar way as in 'kraft pulping' (Someshwar and Pinkerton, 1992, available at: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.592.5534&rep=rep1&type=pdf).

In the patent literature, processes have been described to produce α-cellulose. In these processes, wood chips are digested, at high temperature (> 100°C), by treatment with a mixture of sodium hydroxide (NaOH), sodium sulfide (Na_2S) and sodium sulfite (Na_2SO_3) in various concentrations. During this treatment, the lignin fraction is removed. The product so obtained is extracted washed, concentrated and bleached by treatment with chlorine dioxide (ClO_2). After bleaching, the extract is subjected to a second digestion with sodium hydroxide at lower temperature (< 50°C). The resulting product is centrifuged and washed with oxalic acid to neutralise the residual alkali and to facilitate the extraction of other residuals and colouring impurities. Finally, the extract consists of α-cellulose at a concentration of > 97% (Durchman, 1930; Wayman et al., 1959).

3.1.3.1. Microcrystalline cellulose (E 460(i))

Microcrystalline cellulose (E 460(i)) is prepared by the controlled hydrolysis of highly purified α-cellulose. Hydrolysis is performed with a dilute mineral acid, e.g. hydrochloric acid. Cellulose is thereby converted into an acid-soluble fraction and an acid-insoluble crystalline material. The amorphous regions of the cellulose are completely hydrolysed. Resultant water-soluble cello-oligosaccharides and glucose are removed by subsequent rinsing and filtration. The remaining wet cake contains only pure crystalline regions of natural cellulose. Mechanical shearing in a water slurry is used to free the microcrystals from their fibrous, packed structure, in the form of short, rod-like particles. These are dried and ground to a fine, white, free-flowing crystalline powder (Klose and Glicksman, 1990; Iijima and Takeo, 2000).

Haafiz et al. (2010) described a method for the isolation of microcrystalline cellulose from oil palm empty fruit pulp (OPEFB-pulp). The pulp was hydrolysed with 2.5 N HCl (ratio pulp-liquor 1:20) at 105°C for 30 min under constant agitation. The reaction mixture was filtered and washed repeatedly first with distilled water and subsequently with 5% diluted NH_4OH solution. Finally, distilled water was used to rinse the mixture until it was free from acid. The microcrystalline cellulose so obtained was dried at 105°C under vacuum until constant weight, and further ground into a fine powder, snowy-white in appearance.

3.1.3.2. Powdered cellulose (E 460(ii))

According to Commission Regulation (EU) No 231/2012, powdered cellulose is obtained by purification and mechanical disintegration of α-cellulose.

JECFA (2006a) stated that purified, mechanically disintegrated cellulose is prepared by processing α-cellulose obtained as a pulp from fibrous plant materials; it occurs as a white, odourless substance consisting of fibrous particles which may be compressed into self-binding tablets which disintegrate rapidly in water; it exists in various grades exhibiting degrees of fineness ranging from a dense free-flowing powder to a coarse, fluffy non-flowing material.

In the patent literature, powdered cellulose is described as a product obtained from cellulose, primarily by mechanical procedures such as grinding. It is stated to be a purified, partially depolymerised cellulose, white (white to grey colour scale), odourless, tasteless powder. It is indicated that various methods for obtaining powdered cellulose of different grades have been described. In all

these methods, the cellulose chains are partially degraded, enzymatically or thermally, or by means of using chemical reagents. The amorphous portions of the cellulose are hydrolysed with these treatments and removed. Methods for preparing powdered cellulose are described in patents by Durian et al. (2011) and Yamasaki et al. (2006).

3.1.3.3. Chemically modified celluloses

Chemically modified celluloses (E 461–466), except enzymatically hydrolysed carboxy methyl cellulose (E 469) and cross-linked sodium carboxy methyl cellulose (E 468), are obtained from cellulose as raw material. The base material for E 468 and E 469 is carboxy methyl cellulose (E 466).

The manufacturing processes of modified celluloses are detailed in literature. In general terms, cellulose pulp is dispersed in alkali solution (generally sodium hydroxide, 5–50%) to form alkali cellulose. Alkali celluloses are compounds with given stoichiometric relations between alkali and cellulose (Sjöström, 1993). Subsequently, alkali cellulose is treated with appropriate reagents, under strictly controlled conditions, to substitute the anhydroglucose monomers of the cellulose chain. In this reaction step, the hydroxy groups of the anhydroglucose monomers of the cellulose chain are etherified according to a nucleophilic substitution reaction (S_N2 reaction; Williamson synthesis), a bimolecular reaction with simultaneous a bond-making and a bond-breaking step.

The appropriate etherifying reagents are: (i) in case of methyl cellulose (E 461), methyl chloride; (ii) in case of ethyl cellulose (E 462), ethyl chloride; (iii) in case of ethyl methyl cellulose (E 465) a mixture of ethyl and methyl chloride; (iv) in case of hydroxypropyl cellulose (E 463), propylene oxide; (v) in case of hydroxypropyl methyl cellulose (E 464), a mixture of propylene oxide and methyl chloride.

In the patent literature (Engleman et al., 2014), it is indicated that in the course of the manufacturing of hydroxypropyl methyl cellulose (E 464), propylene chlorohydrin (PCH) can be formed during the process that is aimed to reduce the viscosity of hydroxypropyl methyl cellulose (by adding HCl), via the reaction of HCl with propylene oxide. It is further indicated that PCH can also be formed in the substitution reactor, when propylene oxide and salt react with each other as a secondary reaction, next to the intended reaction of propylene oxide and methyl chloride with alkali cellulose to achieve the methoxy and hydroxypropyl substitutions on the cellulose.

Engleman et al. (2014) described a method for the manufacturing of low molecular weight hydroxyalkyl alkyl cellulose with a reduced concentration of such propylene chlorohydrin or other alkylene halogenohydrins. It is described that alkylene halogenohydrin could be efficiently removed from cellulose ether if extra water was added to the cellulose ether prior to drying, or if steam or a steam mixture was used instead of air, nitrogen or vacuum as the drying medium.

For the manufacturing of additives E 463 and E 464, the hydroxyalkylation of alkali cellulose is not limited to the hydroxyl groups originally present in the system; hydroxyalkylation can proceed at the newly formed hydroxyl groups resulting in hydroxyalkyl chains of varying length and complexity (Klemm et al., 1998; Murray, 2009).

Sodium carboxy methyl cellulose (E 466) is obtained by etherification of alkali cellulose with sodium monochloroacetate (up to 30%) in an alcohol–water medium. During the substitution process, the mixture of alkali cellulose and reagent is heated (50–75°C) and stirred. The DS of the resulting modified cellulose can be controlled by the reaction conditions and use of additives such as organic solvents (isopropanol). Side reactions (e.g. formation of sodium glycolate) can occur, and consume a certain amount of the aqueous alkali. The substitution reaction is followed by purification and washing stages to remove by-products and to achieve the purity levels specified for food additives (Feddersen and Thorp, 1993; Dönges, 1997; Klemm et al., 1998; Mann et al., 1998; Murray, 2009; Heydarzadeh et al., 2009).

According to JECFA (2002), cross-linked sodium carboxy methyl cellulose (E 468) is manufactured by acidifying an aqueous suspension of sodium carboxy methyl cellulose and heating the suspension to achieve cross-linking. The product is then washed and dried. It can also be produced during the manufacture of sodium carboxy methyl cellulose by lowering the pH and heating to produce cross-linking.

According to Swarbrick and Boylan (1990), cross-linked sodium carboxy methyl cellulose (E 468) is made by soaking crude cellulose in sodium hydroxide, and reacting the cellulose with sodium monochloroacetate to form sodium carboxy methyl cellulose. Excess sodium monochloroacetate slowly hydrolyses to glycolic acid and the glycolic acid catalyses the cross-linkage to form cross-linked sodium carboxy methyl cellulose.

Enzymatically hydrolysed carboxy methyl cellulose (E 469) is manufactured by hydrolysis (at 50°C) of carboxy methyl cellulose by an extracellular cellulase enzyme produced by *T. reesei* (now *T. longibrachiatum)*. The enzymatic hydrolysis results in the breakdown of cellulose to D-glucose. The enzymatic hydrolysis depends on DS; hydrolysis decreases with increasing DS. However, treatment of carboxy methyl cellulose with a DS of 0.7 results in complete hydrolysis (Melo and Kennedy, 1993).

3.1.4. Methods of analysis in food

Methods specifically used for analysing celluloses in food are available only for methyl cellulose (E 461) and hydroxypropyl methyl cellulose (E 464) (Harfmann et al., 2007; Turowski et al., 2007). The dried foods were subjected to sequential enzymatic digestion with the use of heat-stable α-amylase, protease, and amyloglycosidase in order to remove starch and proteins. After enzymatic digestion, the solutions were refrigerated for full hydrolysis of the methyl cellulose. The chilled solutions were then filtered and analysed by size-exclusion liquid chromatography (AOAC, 2011).

For the other celluloses (E 460(i), E 460(ii), E 462, E 463, E 465, E 466, E 468, E 469), no food specific analytical methods are available.

In literature, methods are described for the determination of total dietary fibre.

In 1985, the Association of Official Analytical Chemists (AOAC) introduced a standard method for the determination of total dietary fibre (AOAC Official Method 985.29); this method was based on a method described by Prosky et al. (1985). In 1991, AOAC described an extended and optimised gravimetric method for the measurement of total dietary fibre in food (AOAC Official Method 991.43). Both methods were based on the enzymatic removal of starch and protein of the samples by amylase and protease treatment at 90°C and 60°C, respectively. Insoluble dietary fibres are then separated by filtration and high-molecular weight soluble dietary fibres (HMWSDF) precipitated by 78% ethanol and collected by filtration. Both fibre fractions are dried and weighted and collectively give the total dietary fibre content of the sample.

McCleary (2007, 2010); McCleary et al., 2010) elaborated an 'integrated' method (AOAC Method 2009.01) in which the sample was incubated first with α-amylase at 37°C, and then protein was digested at 60°C by protease; subsequently, insoluble and high molecular weight soluble dietary fibres were precipitated at 78% ethanol and finally determined gravimetrically. Non-digestible oligosaccharides (NDO) were measured in the ethanol filtrate by high-performance liquid chromatography (HPLC).

In McCleary et al. (2012) described a new, AOAC-validated, enzymatic-gravimetric method for the analysis of insoluble, soluble and total dietary fibre, inclusive resistant starch and water:alcohol-soluble NDO and polysaccharides with a DP $\geq$ 3. This method was a combination of the Official Methods of Analysis AOAC 985.29 (and its extensions 991.42 and 993.19), 991.43, 2001.03 and 2002.02. In this method, the test substance is treated with pancreatic α-amylase and amyloglucosidase for 16 h at 37°C in a sealed container under agitation. The reaction is terminated by pH adjustment and temporary heating. Protein is then digested with proteinase.

3.1.5. Reaction and fate in food

Proteins and hydrocolloids are known to interact in a variety of ways. Hydrocolloids in general may carry positive or negative charges or be uncharged. Few hydrocolloids carry positive charges and most are negatively charged or uncharged. Environmental conditions such as pH, temperature and ionic strength also influence the interaction (Tolstoguzov, 1991). Cellulose, for example, is a non-ionic polymer, and since it does not carry a charge, the changes in pH do not affect the polymer. carboxy methyl cellulose, however, contains a percentage of anionically charged with a pKa value of 4.0; therefore above pH 4, it is negatively charged. The charge of meat proteins depends strongly upon the pH and they carry an overall positive charge below their isoelectric point (5.0–5.1) and negative charge above. Thus, one can expect no electrostatic interaction between cellulose and meat proteins regardless of the pH, and electrostatic interaction between CMC and meat proteins below a pH of 5.0.

CMC and microcrystalline cellulose (MCC) can be used as fibres in meat batters. Therefore, they can have an impact on the structural characteristics of emulsified sausages that contain large concentrations of proteins that may exceed 15%. Schuh et al. (2013) studied the molecular interactions of meat protein with celluloses using a formulation of Lyoner-style sausages with 0.3–2% CMC/MCC. The addition of CMC (> 0.7%) led to destabilisation of the batter, interfering in the protein network; however, MCC was compatible with the protein matrix and improved firmness without affecting the water binding capacity.

For modified celluloses, different substitutions on the cellulose backbone, as anionic groups in CMC or certain hydrophobicity in hydroxypropyl methyl cellulose (HPMC), lead to macromolecules with different properties compared to native cellulose.

Modified celluloses affect gluten network conformation, depending on the interactions on the type of hydrocolloid and NaCl addition.

Correa and Cristina Ferrero (2014) studied the interaction of modified celluloses (MCC, CMC, HPMC) and pectins with gluten proteins. The modified celluloses were employed at 1.5% (flour basis) of wheat bread dough making. They have reported that they can induce changes on gluten network during their formation, affecting strongly the secondary conformation of the proteins, the CMC dough showing the smallest percentage of α-helix conformation and the highest unfolded structures. CMC is an anionic molecule that could interact with gluten proteins through electrostatic forces, leading to a less cross-linked structure. While MCC samples showed similar structural characteristics to the control, samples with CMC and HPMC led to a more filamentous and oriented gluten network. CMC, as a negatively charged molecule, could establish electrostatic interactions in the absence of NaCl, while for HPMC, the addition of NaCl favoured the hydrophobic interactions.

CMC is widely used as a stabiliser and thickener in the food industry. Bayarri and Costell, 2010, reported the behaviour of CMC in dairy desserts, which are complex systems where CMC interactions with carbohydrates and milk proteins can be studied. The influence of CMC concentration (0.75%, 1.00%, 1.25% and 1.50% w/w) and type of dispersing media (aqueous solution, skimmed milk and whole milk) on the viscoelastic properties of aqueous and milk systems were studied. Both parameters affected the viscoelastic behaviour, which ranged from fluid-like to weak gel. Concentrations of CMC below 0.75% w/w did not have any effect. The highest CMC concentration (1.5% w/w) the most affected systems were the whole milk samples with higher values for the viscoelastic parameters and the aqueous solutions the less affected, suggesting some substantial interaction between the protein adsorbed in oil droplet of the milk and CMC.

Xue and Ngadi (2009) studied the functionality of methyl cellulose (MC) and CMC in batter systems during thermal processing, and the synergistic effects of the hydrocolloids and different flour blend combinations on the thermal properties of the different batter systems. For this study, three flour blends were prepared with rice, wheat and corn flours, with 2.5% salt and 3.1% leavening agent (1.78% sodium acid pyrophosphate/1.32% sodium bicarbonate). The MC and CMC powders were first dispersed and mixed in with the total amount of cold distilled water required for the batter. Afterwards, the hydrocolloid was totally dissolved, and the dry ingredients (flour, salt and leavening) were added to the hydrocolloid solution and manually mixed thoroughly until the batter was uniform and free of lumps. Addition of these hydrocolloids increased the gelatinisation temperatures but depressed the glass transition temperatures of the resulting batters. Batters with MC showed increased DHm (melting enthalpy) for all the thermal processes, whereas batters with CMC only showed significant effect on total melting enthalpies DHm for cooked samples. To simulate processing of battered products that are first frozen before they are cooked (namely freezing–cooking (FC) process), the samples were first rapidly cooled to 50°C at the rate of 20°C/min, then heated to 120°C at 10°C/min.

The effect of these hydrocolloids on glass transition temperature was more pronounced in raw samples (FC process) than in cooked samples and increased with increasing levels of CMC and MC used in the formulations.

Floury et al. (2003) observed, when studying the effect of high-pressure homogenisation (at 350 mPa) on methyl cellulose as a food emulsifier, that microphase separation occurred at homogenisation temperatures $>$ 63°C. At these temperatures, methyl cellulose lost a great part of its stabilising properties and precipitated. The phenomenon was explained by the fact that methyl cellulose was subject to thermoreversible gelation upon increasing the temperature due to the fact that the polymer its phase-transition temperature (Chevillard and Axelos, 1997).

3.2. Authorised uses and use levels

Maximum levels of microcrystalline cellulose (E 460(i)), powdered cellulose (E 460(ii)), methyl cellulose (E 461), ethyl cellulose (E 462), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464), ethyl methyl cellulose (E 465), sodium carboxy methyl cellulose (E 466), cross-linked sodium carboxy methyl cellulose (E 468) and enzymatically hydrolysed carboxy methyl cellulose (E 469) have been defined in Annex II to Regulation (EC) No 1333/2008 on food additives, as amended. In this document, these levels are named maximum permitted levels (MPLs).

Currently, microcrystalline cellulose (E 460(i)), powdered cellulose (E 460(ii)), methyl cellulose (E 461), ethyl cellulose (E 462), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464), ethyl methyl cellulose (E 465), sodium carboxy methyl cellulose (E 466) and enzymatically hydrolysed carboxy methyl cellulose (E 469) are authorised food additives in the EU at *quantum satis* (QS), in almost all authorised food categories listed in Table 13. They are also included in Group I of food additives authorised at QS. Cross-linked sodium carboxy methyl cellulose (E 468) is an authorised food additive in the EU at levels of 30,000–50,000 mg/kg in three food categories.

Table 13 summarises foods that are permitted to contain E 460–466 and E 468 and E 469 and the corresponding MPLs as set by Annex II to Regulation (EC) No 1333/2008.

Table 13: MPLs of E 460–466 and E 468 and E 469 in foods according to the Annex II to Regulation (EC) No 1333/2008

Food category number	Food category name	E-number	Restrictions/exceptions	MPL (mg/L or mg/kg as appropriate)
01.3	Unflavoured fermented milk products, heat-treated after fermentation	Group I		*Quantum satis*
01.4	Flavoured fermented milk products including heat-treated products	Group I		*Quantum satis*
01.6.1	Unflavoured pasteurised cream (excluding reduced fat creams)	E 466		*Quantum satis*
01.6.2	Unflavoured live fermented cream products and substitute products with a fat content of less than 20%	E 460, E 466		*Quantum satis*
01.6.3	Other creams	Group I		*Quantum satis*
01.7.1	Unripened cheese excluding products falling in category 16	E 460(ii)	Only grated and sliced mozzarella	*Quantum satis*
01.7.1	Unripened cheese excluding products falling in category 16	Group I	Except mozzarella	*Quantum satis*
01.7.2	Ripened cheese	E 460	Only sliced and grated ripened cheese	*Quantum satis*
01.7.4	Whey cheese	E 460(ii)	Only grated and sliced cheese	*Quantum satis*
01.7.5	Processed cheese	Group I		*Quantum satis*
01.7.6	Cheese products (excluding products falling in category 16)	Group I		*Quantum satis*
01.7.6	Cheese products (excluding products falling in category 16)	E 460	Only grated and sliced ripened products and unripened products	*Quantum satis*
01.8	Dairy analogues, including beverage whiteners	Group I		*Quantum satis*
02.2.2	Other fat and oil emulsions including spreads as defined by Council Regulation (EC) No 1234/2007 and liquid emulsions	Group I		*Quantum satis*
02.3	Vegetable oil pan spray	Group I		*Quantum satis*
03	Edible ices	Group I		*Quantum satis*

Food category number	Food category name	E-number	Restrictions/exceptions	MPL (mg/L or mg/kg as appropriate)
04.1.1	Entire fresh fruit and vegetables	E 464	Only for citrus fruit, melons and pomegranates in order to: • repeat all or some of the mandatory information particulars required by the Union legislation and/or national law and/or • provide on a voluntary basis brand name, production method, PLU-code, QR-code and/or barcode	10
04.2.1	Dried fruit and vegetables	Group I		*Quantum satis*
04.2.2	Fruit and vegetables in vinegar, oil, or brine	Group I		*Quantum satis*
04.2.4.1	Fruit and vegetable preparations excluding compote	Group I		*Quantum satis*
04.2.5.4	Nut butters and nut spreads	Group I		*Quantum satis*
04.2.6	Processed potato products	Group I		*Quantum satis*
05.1	Cocoa and Chocolate products as covered by Directive 2000/36/EC	Group I	Only energy-reduced or with no added sugar	*Quantum satis*
05.2	Other confectionery including breath freshening microsweets	Group I		*Quantum satis*
05.3	Chewing gum	Group I		*Quantum satis*
05.4	Decorations, coatings and fillings, except fruit-based fillings covered by category 4.2.4	Group I		*Quantum satis*
06.2.2	Starches	Group I		*Quantum satis*
06.3	Breakfast cereals	Group I		*Quantum satis*
06.4.2	Dry pasta	Group I	Only gluten free and/or pasta intended for hypoproteic diets in accordance with Directive 2009/39/EC	*Quantum satis*
06.4.4	Potato gnocchi	Group I	Except fresh refrigerated potato gnocchi	*Quantum satis*
06.4.5	Fillings of stuffed pasta (ravioli and similar)	Group I		*Quantum satis*
06.5	Noodles	Group I		*Quantum satis*
06.6	Batters	Group I		*Quantum satis*
06.7	Pre-cooked or processed cereals	Group I		*Quantum satis*
07.1	Bread and rolls	Group I	Except products in 7.1.1 and 7.1.2	*Quantum satis*
07.2	Fine bakery wares	Group I		*Quantum satis*
08.3.1	Non-heat-treated meat products	Group I		*Quantum satis*
08.3.2	Heat-treated meat products	Group I	Except *foie gras, foie gras entier, blocs de foie gras, Libamáj, libamáj egészben, libamáj tömbben*	*Quantum satis*
08.3.3	Casings and coatings and decorations for meat	Group I		*Quantum satis*

Food category number	Food category name	E-number	Restrictions/exceptions	MPL (mg/L or mg/kg as appropriate)
09.2	Processed fish and fishery products including molluscs and crustaceans	Group I		*Quantum satis*
09.3	Fish roe	Group I	Only processed fish roe	*Quantum satis*
10.2	Processed eggs and egg products	Group I		*Quantum satis*
11.2	Other sugars and syrups	Group I		*Quantum satis*
11.4.1	Table-top sweeteners in liquid form	E 460(i), E 463, E 464, E 465, E 466		*Quantum satis*
11.4.2	Table-top sweeteners in powder form	E 460, E 461, E 463, E 464, E 465, E 466		*Quantum satis*
11.4.2	Table-top sweeteners in powder form	E 468		50,000
11.4.3	Table-top sweeteners in tablets	E 460, E 461, E 463, E 464, E 465, E 466		*Quantum satis*
11.4.3	Table-top sweeteners in tablets	E 468		50,000
12.1.2	Salt substitutes	Group I		*Quantum satis*
12.2.1	Herbs and spices	E 460	Only when dried	
12.2.2	Seasonings and condiments	Group I		*Quantum satis*
12.3	Vinegars	Group I		*Quantum satis*
12.4	Mustard	Group I		*Quantum satis*
12.5	Soups and broths	Group I		*Quantum satis*
12.6	Sauces	Group I		*Quantum satis*
12.7	Salads and savoury-based sandwich spreads	Group I		*Quantum satis*
12.8	Yeast and yeast products	Group I		*Quantum satis*
12.9	Protein products, excluding products covered in category 1.8	Group I		*Quantum satis*
13.1.5.1	Dietary foods for infants for special medical purposes and special formulae for infants	E 466	From birth onwards in products for the dietary management of metabolic disorders	10,000
13.1.5.2	Dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC	E 466	From birth onwards in products for the dietary management of metabolic disorders	10,000
13.2	Dietary foods for special medical purposes defined in Directive 1999/21/EC (excluding products from food category 13.1.5)	Group I		*Quantum satis*
13.3	Dietary foods for weight control diets intended to replace total daily food intake or an individual meal (the whole or part of the total daily diet)	Group I		*Quantum satis*

Food category number	Food category name	E-number	Restrictions/exceptions	MPL (mg/L or mg/kg as appropriate)
13.4	Foods suitable for people intolerant to gluten as defined by Regulation (EC) No 41/2009	Group I	Including dry pasta	*Quantum satis*
14.1.2	Fruit juices as defined by Directive 2001/112/EC and vegetable juices	Group I	Only vegetable juices	*Quantum satis*
14.1.3	Fruit nectars as defined by Directive 2001/112/EC and vegetable nectars and similar products	Group I	Only vegetable nectars	*Quantum satis*
14.1.3	Fruit nectars as defined by Directive 2001/112/EC and vegetable nectars and similar products	E 466	Only traditional Swedish and Finnish fruit syrups from citrus	*Quantum satis*
14.1.4	Flavoured drinks	Group I		*Quantum satis*
14.1.5.2	Other	Group I	Excluding unflavoured leaf tea; including flavoured instant coffee	*Quantum satis*
14.2.3	Cider and perry	Group I		*Quantum satis*
14.2.4	Fruit wine and made wine	Group I		*Quantum satis*
14.2.5	Mead	Group I		*Quantum satis*
14.2.6	Spirit drinks as defined in Regulation (EC) No 110/2008	Group I	Except whisky or whiskey	*Quantum satis*
14.2.7.1	Aromatised wines	Group I		*Quantum satis*
14.2.7.2	Aromatised wine-based drinks	Group I		*Quantum satis*
14.2.7.3	Aromatised wine-product cocktails	Group I		*Quantum satis*
14.2.8	Other alcoholic drinks including mixtures of alcoholic drinks with non-alcoholic drinks and spirits with less than 15% of alcohol	Group I		*Quantum satis*
15.1	Potato-, cereal-, flour- or starch-based snacks	Group I		*Quantum satis*
15.2	Processed nuts	Group I		*Quantum satis*
16	Desserts excluding products covered in category 1, 3 and 4	Group I		*Quantum satis*
17.1[(a)]	Food supplements supplied in a solid form including capsules and tablets and similar forms, excluding chewable forms	Group I		*Quantum satis*
17.1[(a)]	Food supplements supplied in a solid form including capsules and tablets and similar forms, excluding chewable forms	E 468		30,000
17.2[(a)]	Food supplements supplied in a liquid form	Group I		*Quantum satis*
17.3[(a)]	Food supplements supplied in a syrup-type or chewable form	Group I		*Quantum satis*
18	Processed foods not covered by categories 1–17, excluding foods for infants and young children	Group I		*Quantum satis*

MPL: maximum permitted level.
(a): FCS 17 refers to food supplements as defined in Directive 2002/46/EC of the European Parliament and of the Council excluding food supplements for infants and young children.

According to Annex III, Part 1 of Regulation (EC) No 1333/2008, E 460–466 are also authorised as carriers in all food additives at QS; E 468 is authorised as a carrier in sweeteners at QS and E 469 is authorised as a carrier in all food additives at QS.

According to Annex III, Part 2 of Regulation (EC) No 1333/2008, E 460, E 461, E 462, E 463, E 464, E 465, E 466 and E 469 are authorised as food additives other than carriers at QS, in all food additive preparations.

According to Annex III, Part 3 of Regulation (EC) No 1333/2008, E 460, E 461, E 463, E 464 and E 466 are authorised as food additives including carriers in food enzymes at QS, while E 462, E 465 and E 469 are authorised as food additives at QS levels but cannot be used as carriers.

According to Annex III, Part 4 of Regulation (EC) No 1333/2008, E 460, E 461, E 462, E 463, E 464, E 465, E 466 and E 469 are authorised as food additives including carriers in all food flavourings at QS.

In addition, according to Annex III, Part 5, Section A of Regulation (EC) No 1333/2008, E 460–466 and E 469 are authorised to be used as food additives including carriers in all nutrients at QS except for nutrients intended to be used in foodstuffs for infants and young children listed in point 13.1 of Part E of Annex II.

Finally, according to Annex III, Part 5, Section B of Regulation (EC) No 1333/2008, E 466 is authorised as a food additive for uses in nutrient preparations under the condition that the maximum level in foods mentioned in point 13.1 of Part E of Annex II is not exceeded,[11] in all nutrients in dietary foods for infants and young children for special medical purposes as defined in Directive 1999/21/EC, nutrients intended to be used in foodstuffs for infants and young children listed in point 13.1 of Part E of Annex II.

3.3. Exposure data

3.3.1. Reported use levels or data on analytical levels

Most food additives in the EU are authorised at a specific MPL. However, a food additive may be used at a lower level than the MPL. Therefore, information on actual use levels is required for performing a more realistic exposure assessment, especially for those food additives for which no MPL is set and which are authorised according to *QS*.

In the framework of Regulation (EC) No 1333/2008 on food additives and of Commission Regulation (EU) No 257/2010 regarding the re-evaluation of approved food additives, EFSA issued public calls,[12,13] for occurrence data (usage level and/or concentration data) on microcrystalline cellulose (E 460(i)), powdered cellulose (E 460(ii)), methyl cellulose (E 461), ethyl cellulose (E 462), methyl cellulose (E 464), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464), ethyl methyl cellulose (E 465), sodium carboxy methyl cellulose (E 466), cross-linked sodium carboxy methyl cellulose (E 468) and enzymatically hydrolysed carboxy methyl cellulose (E 469). In response to this public call, updated information on the actual use levels of celluloses (E 460–466, E 468 and E 469) in foods was made available to EFSA by industry. One analytical data on the concentration of these food additives in foods was made available by Member State (MS).

3.3.1.1. Summarised data on reported use levels in foods provided by industry

Industry provided EFSA with data on use levels (n = 1,177) of celluloses (E 460–466, E 468 and E 469) in foods for 57 out of the 84 food categories in which celluloses (E 460–466, E 468 and E 469) are authorised.

Updated information on the actual use levels of celluloses (E 460–466, E 468 and E 469) in foods was made available to EFSA by the Association of the European Self-Medication Industry (AESGP), Aviko, Dr Loges Naturheilkunde neu entdecken, the European Dairy Association (EDA), the European Federation of Associations of Health Products Manufacturers (EHPM), FoodDrinkEurope (FDE), Food Supplements Europe (FSE), the International Chewing Gum Association (ICGA), Kruger GmbH & Co and the Organisation des Fabricants de produits Cellulosiques Alimentaires (OFCA) [Documentation provided to EFSA, n. 1–10].

The Panel noted that some data providers (e.g. OFCA) are not food industry using celluloses in their food products but food additive producers. Usage levels reported by food additive producers should not be considered at the same level as those provided by food industry. Food additive producers might recommend usage levels to the food industry but the final levels might, ultimately, differ, unless food additive producers confirm that these levels are used by food industry. In all other

[11] 10,000 mg/kg.
[12] http://www.efsa.europa.eu/sites/default/files/consultation/151012.pdf
[13] http://www.efsa.europa.eu/sites/default/files/consultation/ans091123.pdf

cases, data from food additive producers will only be used in the MPL scenario in case of QS authorisation and no data are available from food industry or MSs in order to have the most complete exposure estimates. In any case, all usage data provided will be acknowledged in the appendices.

Appendix A provides data on the use levels of celluloses (E 460–466, E 468 and E 469) in foods as reported by industry.

3.3.1.2. Summarised data on concentration levels in foods submitted by Member States

In total, one analytical result was reported to EFSA by Germany, on a meat product sampled and analysed in 2013, with a level of 3,700 mg/kg. This meat preparation was not taken into account in the exposure estimates.

Complete information on the methods of analysis (e.g. validation) was not made available to EFSA, but the sample was derived from accredited laboratory.

3.3.2. Summarised data extracted from the Mintel Global New Products Database

The Mintel GNPD is an online database which monitors product introductions in consumer packaged goods markets worldwide. It contains information of over 2 million food and beverage products of which more than 900,000 are or have been available on the European food market. Mintel started covering EU's food markets in 1996, currently having 20 out of its 28 member countries and Norway presented in the Mintel GNPD.[14]

For the purpose of this Scientific Opinion, the Mintel GNPD[15] was used for checking the labelling of products containing E 460–466, E 468 and E 469 within the EU's food products as the Mintel GNPD shows the compulsory ingredient information presented in the labelling of products.

According to Mintel, celluloses (E 460–466, E 468 and E 469) are labelled on more than 18,000 products out of which around 11,500 between 2012 and 2017.

Appendix B presents the percentage of the food products labelled with celluloses (E 460–466, E 468 and E 469) out of the total number of food products per food subcategory according to the Mintel GNPD food classification. The percentages ranged from less than 0.1% in many food subcategories to 27.7% in Mintel's GNPD subcategory 'Vitamins and dietary supplements'. The average percentage of foods labelled to contain celluloses (E 460–466, E 468–469) was 2.3%.

3.3.3. Food consumption data used for exposure assessment

EFSA Comprehensive European Food Consumption Database

Since 2010, the EFSA Comprehensive European Food Consumption Database (Comprehensive Database) has been populated with national data on food consumption at a detailed level. Competent authorities in the European countries provide EFSA with data on the level of food consumption by the individual consumer from the most recent national dietary survey in their country (cf. Guidance of EFSA on the 'Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment' (EFSA, 2011a). New consumption surveys[16] added in the Comprehensive database were also taken into account in this assessment.[10]

The food consumption data gathered by EFSA were collected by different methodologies and thus direct country-to-country comparisons should be interpreted with caution. Depending on the food category and the level of detail used for exposure calculations, uncertainties could be introduced owing to possible subjects' underreporting and/or misreporting of the consumption amounts. Nevertheless, the EFSA Comprehensive Database represents the best available source of food consumption data across Europe at present.

Food consumption data from the following population groups: infants, toddlers, children, adolescents, adults and the elderly were used for the exposure assessment. For the present assessment, food consumption data were available from 33 different dietary surveys carried out in 19 European countries (Table 14).

[14] Missing Bulgaria, Cyprus, Estonia, Latvia, Lithuania, Luxembourg, Malta and Slovenia.
[15] http://www.gnpd.com/sinatra/home/ accessed on 31/08/2017.
[16] Available online: http://www.efsa.europa.eu/en/press/news/150428.htm

Table 14: Population groups considered for the exposure estimates of celluloses

Population	Age range	Countries with food consumption surveys covering more than one day
Infants	From 12 weeks up to and including 11 months of age	Bulgaria, Denmark, Finland, Germany, Italy, UK
Toddlers[a]	From 12 months up to and including 35 months of age	Belgium, Bulgaria, Denmark, Finland, Germany, Italy, the Netherlands, Spain, UK
Children[b]	From 36 months up to and including 9 years of age	Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Latvia, Netherlands, Spain, Sweden, UK
Adolescents	From 10 years up to and including 17 years of age	Austria, Belgium, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Italy, Latvia, Netherlands, Spain, Sweden, UK
Adults	From 18 years up to and including 64 years of age	Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Netherlands, Romania, Spain, Sweden, UK
The elderly[b]	From 65 years of age and older	Austria, Belgium, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Netherlands, Romania, Sweden, UK

(a): 'Toddlers' in the EFSA Comprehensive Database corresponds to 'young children' in Regulations (EC) No 1333/2008 and (EU) No 609/2013.

(b): The terms 'children' and 'the elderly' correspond, respectively, to 'other children' and the merge of 'elderly' and 'very elderly' in the Guidance of EFSA on the 'Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment' (EFSA, 2011a).

Consumption records were codified according to the FoodEx classification system (EFSA, 2011b). Nomenclature from the FoodEx classification system has been linked to the Food Classification System (FCS) as presented in Annex II of Regulation (EC) No 1333/2008, part D, to perform exposure estimates. In practice, FoodEx food codes were matched to the FCS food categories.

Food categories selected for the exposure assessment of celluloses (E 460–466, E 468 and E 469)

The food categories in which the use of celluloses is authorised were selected from the nomenclature of the EFSA Comprehensive Database (FoodEx classification system), at the most detailed level possible (up to FoodEx Level 4) (EFSA, 2011b).

Some food categories are not referenced in the EFSA Comprehensive Database and could therefore not be taken into account in the present estimate. This is the case for 12 food categories and may result in an underestimation of the exposure. The food categories which were not taken into account are described below (in ascending order of the FCS codes):

- 01.7.6 Cheese products;
- 02.3 Vegetable oil pan spray;
- 06.6 Batters;
- 06.7 Pre-cooked or processed cereals;
- 08.3.3 Casings and coatings and decorations for meat;
- 12.1.2 Salt substitutes;
- 14.1.3 Fruit nectars, only vegetable nectars;
- 14.1.3 Fruit nectars, only traditional Swedish and Finnish fruit syrups from citrus;
- 14.2.4 Fruit wine and made wine;
- 14.2.5 Mead;
- 14.2.7.2. Aromatised wine-based drinks;
- 14.2.7.3. Aromatised wine-product cocktails.

For the following food categories, the restrictions/exceptions which apply to the use of celluloses (E 460–466, E 468 and E 469) could not be taken into account, and therefore the whole food category was considered in the exposure assessment. This is the case for three food categories and may result in an overestimation of the exposure:

- 07.1 Bread and rolls, except products in 7.1.1 and 7.1.2;
- 09.3 Fish roe, only processed fish roe;

Celluloses (E 460–466, E 468 and E 469) are also allowed in FC 13.2, 13.3, 13.4 and 18. Food items under food categories 13.2, 13.3 and 13.4 consumed by population groups – children, adolescents, adults and the elderly – may be very diverse and, in addition, there is very limited information on their consumption. Therefore, eating occasions belonging to the food categories 13.2, 13.3 and 13.4 were reclassified under food categories in accordance to their main component. The use levels available for food categories 13.2, 13.3 and 13.4 were not considered for the exposure assessment.

For all scenarios, additional food categories were not taken into account because no concentration data were provided for these food categories to EFSA (Appendix C). Overall, for the maximum level exposure scenario, 48 food categories were included, while for the refined scenarios, 26 food categories were included in the present exposure assessment to celluloses (E 460–466, E 468 and E 469). For the remaining food categories, the refinements considering the restrictions/exceptions as set in Annex II to Regulation No 1333/2008 were applied (Appendix C).

3.4. Exposure estimate(s)

3.4.1. Exposure to celluloses from their use as food additives

The Panel estimated chronic exposure to celluloses (E 460–466, E 468 and E 469) for the following population groups: infants, toddlers, children, adolescents, adults and the elderly. Dietary exposure to celluloses was calculated by multiplying celluloses concentrations for each food category (Appendix C) with their respective consumption amount per kilogram of body weight for each individual in the Comprehensive Database. The exposure per food category was subsequently added to derive an individual total exposure per day. These exposure estimates were averaged over the number of survey days, resulting in an individual average exposure per day for the survey period. Dietary surveys with only one day per subject were excluded, as they are considered as not adequate to assess repeated exposure.

This was carried out for all individuals per survey and per population group, resulting in distributions of individual exposure per survey and population group (Table 3). Based on these distributions, the mean and 95th percentile of exposure were calculated per survey for the total population and per population group. High percentile exposure was only calculated for those population groups where the sample size was sufficiently large to allow calculation of the 95th percentile of exposure (EFSA, 2011a). Therefore, in the present assessment, high levels of exposure for infants from Italy and for toddlers from Belgium, Italy and Spain were not included.

Exposure assessment to celluloses (E 460–466, E 468 and E 469) was carried out by the ANS Panel based on (1) maximum levels of data provided to EFSA (defined as the maximum level exposure assessment scenario), and (2) reported use levels (defined as the refined exposure assessment scenario) as provided by industry. These two scenarios are discussed in detail below.

These scenarios do not consider the consumption of food supplements (FC 17.1, FC 17.2 and FC 17.3), nor the consumption of foods for special medical purposes (FSMP), which are covered in additional refined exposure scenarios detailed below (*food supplements consumers only scenario* and *food for special medical purposes consumer only scenario*).

Considering that the food category 18 (Processed foods not covered by categories 1–17, excluding foods for infants and young children) is extremely unspecific (e.g. composite foods), processed foods, prepared, or composite dishes belonging to the food category 18 were reclassified under food categories in accordance to their main component. Therefore, food category 18 is not taken into account as contributor to the total exposure estimates.

Concerning the uses of celluloses (E 460–466, E 468 and E 469) as carriers, there might be food categories where celluloses are used according to Annex III and not to Annex II. These food categories can only be addressed by analytical data or limits set in the Regulation (EC) No 1333/2008. According to Annex III, Parts 1, 2, 3, 4 and 5 of Regulation (EC) No 1333/2008, celluloses (E 460–466, E 468 and E 469) are also authorised at QS; as no data were made available to EFSA, this added dietary exposure could not be taken into account in the any of the exposure scenarios.

3.4.1.1. Maximum level exposure assessment scenario

The regulatory maximum level exposure assessment scenario is based on the MPLs as set in Annex II to Regulation (EC) No 1333/2008. As celluloses (E 460–466, E 468 and E 469) are authorised according to QS in almost all food categories, a 'maximum level exposure assessment' scenario was

estimated based on the maximum reported use levels provided by industry (food industry and food additive producers) as described in the EFSA Conceptual framework (EFSA ANS Panel, 2014).

A possible additional exposure from the use of celluloses (E 460–466, E 468 and E 469) in accordance with Annex III to Regulation (EC) No 1333/2008 (Part 1, 3, 5) was not considered in the maximum level exposure assessment scenario. Despite this, the Panel considers the exposure estimates derived following this scenario as the most conservative, as it is assumed that the population group will be exposed to celluloses (E 460–466, E 468 and E 469) present in food at maximum reported use levels over a longer period of time.

3.4.1.2. Refined exposure assessment scenario

The refined exposure assessment scenario is based on use levels reported by food industry. This exposure scenario can consider only food categories for which the above data were available to the Panel.

Appendix C summarises the concentration levels of celluloses (E 460–466, E 468 and E 469) used in the refined exposure assessment scenario. Based on the available data set, the Panel calculated two refined exposure estimates based on different model populations:

- The brand-loyal consumer scenario: It was assumed that a consumer is exposed long-term to celluloses (E 460–466, E 468 and E 469) present at the maximum reported use level for one food category. This exposure estimate was calculated as follows:
  - Combining food consumption with the maximum of the reported use levels, for the main contributing food category at the individual level.
  - Using the mean of the typical reported use levels, for the remaining food categories.
- The non-brand-loyal consumer scenario: It was assumed that a consumer is exposed long-term to celluloses (E 460–466, E 468 and E 469) present at the mean reported use level in food. This exposure estimate was calculated using the mean of the typical reported use levels for all food categories.

3.4.1.3. Specific exposure assessment scenario

- *Food supplements consumers only* scenario: celluloses (E 460–466, E 468 and E 469) are authorised in the food category 17 (i.e. FC 17.1, 17.2, 17.3) (Table 13) Food supplements as defined in Directive 2002/46/EC excluding food supplements for infants and young children. As exposure via food supplements may deviate largely from the one via food, and the number of food supplement consumers may be low depending on populations and surveys, an additional scenario was calculated in order to reflect additional exposure to food additives from food supplements compared to exposure to food additives excluding these sources. This scenario was estimated as follow:
  - Consumers only of food supplements were assumed to be exposed to a food additive present at the maximum reported usage on a daily basis via consumption of food supplements. For the remaining food categories, the mean of the typical reported use levels was used.

As food category 17 does not consider food supplements for infants and toddlers as defined in the legislation, exposure to celluloses (E 460–466, E 468 and E 469) from food supplements is not estimated for these two population groups.

- *FSMP scenario consumers only*: as E 466 is also authorised in the FC 13.1.5 (13.1.5.1 and 13.1.5.2), an additional exposure assessment scenario taking into account this food category was performed to estimate the exposure of infants and toddlers who may eat and drink these FSMP.

  The consumption of these foods under FC 13.1.5 is not reported in the EFSA Comprehensive database. To consider the exposure to food additives via consumption of these foods, the Panel assumed that the amount of FSMP consumed by infants and toddlers resembles that of comparable foods for infants and toddlers from the general population. Thus, the consumption of FSMP categorised as food category 13.1.5 was assumed to equal that of formulae and food products categorised as food categories 13.1.1, 13.1.2, 13.1.3 and 13.1.4.

  The Panel noted that no data were submitted for the food categories 13.1.5.1 and 13.1.5.2, thus, the FSMP exposure assessment scenario for consumers only was performed using the

MPLs of E 466 for these two food categories; for the remaining food categories, the mean of the typical reported use levels was used.
Certain FSMP consumed by other population groups (children, adolescents, adults and the elderly) may be very diverse; they cannot be considered because of very limited information on consumption. Eating occasions belonging to the food categories 13.2, 13.3, 13.4 were therefore reclassified under food categories in accordance to their main component.

3.4.1.4. Dietary exposure to celluloses (E 460–466, E 468 and E 469)

Table 15 summarises the estimated exposure to celluloses from their use as food additives in six population groups (Table 14) according to the different exposure scenarios (Section 3.4.1). Detailed results per population group and survey are presented in Appendix D.

Table 15: Summary of anticipated exposure to celluloses (E 460–466, E 468 and E 469) from their use as food additives in the maximum level exposure assessment scenario and in the refined exposure scenarios, in six population groups (minimum–maximum across the dietary surveys in mg/kg bw per day)

	Infants (12 weeks–11 months)	Toddlers (12–35 months)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
Maximum level exposure assessment scenario						
Mean	22–135	103–546	138–410	65–260	58–157	55–116
High level (95th percentile)	60–394	259–718	270–745	136–460	120–303	109–190
Refined estimated exposure assessment scenario						
Brand-loyal scenario						
Mean	5–50	15–190	44–177	27–126	20–67	18–37
High level (95th percentile)	30–186	42–506	112–387	86–274	47–180	37–80
Non-brand-loyal scenario						
Mean	2–18	5–64	11–58	7–40	7–23	7–16
High level (95th percentile)	13–55	14–111	30–103	21–73	16–48	14–29

bw: body weight.

From the *maximum level exposure assessment scenario*, mean exposure to celluloses (E 460–466, E 468 and E 469) from their use as food additives ranged from 22 mg/kg body weight (bw) per day in infants to 546 mg/kg bw per day in toddlers. The 95th percentile of exposure to celluloses (E 460–466, E 468 and E 469) ranged from 60 mg/kg bw per day in infants to 745 mg/kg bw per day in children.

From the *refined estimated exposure scenario*, in the *brand-loyal scenario*, mean exposure to celluloses (E 460–466, E 468 and E 469) from their use as food additives ranged from 5 mg/kg bw per day in infants to 190 mg/kg bw per day in toddlers. The high exposure to celluloses (E 460–466, E 468 and E 469) ranged from 30 mg/kg bw per day in infants to 506 mg/kg bw per day in toddlers. In the *non-brand-loyal scenario*, mean exposure to celluloses (E 460–466, E 468 and E 469) from their use as food additives ranged from 2 mg/kg bw per day in infants to 64 mg/kg bw per day in toddlers. The 95th percentile of exposure to celluloses (E 460–466, E 468 and E 469) ranged from 13 mg/kg bw per day in infants to 111 mg/kg bw per day in toddlers.

From the refined estimated exposure scenario taking into account FSMP (FC 13.1.5.1 and 13.1.5.2) in which E 466 is authorised, consumers only, mean exposure to celluloses from their uses as food additives ranged for infants between 4 and 508 mg/kg bw per day and between 6 and 154 mg/kg bw per day for toddlers. The 95th percentile of exposure ranged for infants between 14 and 1,557 mg/kg bw per day, and for toddlers between 14 and 557 mg/kg bw per day.

For the food supplement consumers only, mean exposure to celluloses (E 460–466, E 468 and E 469) from their use as food additives ranged between 23 and 332 mg/kg bw per day across the different population classes of children, adolescents, adults and the elderly. The 95th percentile of exposure to celluloses (E 460–466, E 468 and E 469) ranged between 78 and 448 mg/kg bw per day across the same population groups.

3.4.1.5 Main food categories contributing to exposure to celluloses (E 460–466, E 468–469)

Main food categories contributing to exposure to celluloses (E 460–466, E 468–469) using the maximum level exposure assessment scenario

From the *maximum level exposure assessment scenario*, the main contributing food categories to the total mean exposure estimates were breakfast cereals and fine bakery wares for infants and bread and rolls, flavoured fermented milk products and flavoured drinks for toddlers. For children, adolescents and adults, the main contributing food categories were bread and rolls, fine bakery wares and flavoured drinks; while, for the elderly, the main contributing food category was bread and rolls (see Appendix E for more details).

Main food categories contributing to exposure to celluloses (E 460–466, E 468–469) using the refined exposure assessment scenario

The main contributing food categories for the *refined estimated exposure scenario*, *brand-loyal scenario* were bread and rolls, sauces and processed fruits and vegetables for infants; bread and rolls, fine bakery wares and flavoured drinks were the main contributing food categories for the other population groups: toddlers; children, adolescents, adults and the elderly. In the *non-brand-loyal scenario*, the main contributing food categories were bread and rolls, processed fruits and vegetables and fine bakery wares for infants and toddlers. For children, adolescents and adults, the main contributing food categories were bread and rolls, fine bakery wares and flavoured drinks; while for the elderly, the main contributing food categories were bread and rolls and processed fruits and vegetables (see Appendix E for more details).

Appendix E can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2018.5047

3.4.1.6. Uncertainty analysis

Uncertainties in the exposure assessment of celluloses have been discussed above. In accordance with the guidance provided in the EFSA opinion related to uncertainties in dietary exposure assessment (EFSA, 2006), the following sources of uncertainties have been considered and summarised in Table 16.

Table 16: Qualitative evaluation of influence of uncertainties on the dietary exposure estimate

Sources of uncertainties	Direction[(a)]
Consumption data: different methodologies/representativeness/underreporting/ misreporting/no portion size standard	+/–
Use of data from food consumption survey of a few days to estimate long-term (chronic) exposure for high percentiles (95th percentile)	+
Correspondence of reported use levels to the food items in the EFSA Comprehensive Food Consumption Database: uncertainties to which types of food the levels refer to	+/–
Food categories selected for the exposure assessment: exclusion of food categories due to missing FoodEx linkage (n = 12/84 food categories)	–
Food categories selected for the exposure assessment: inclusion of one food category without considering the restriction/exception	+
Food categories included in the exposure assessment: n = 48 food categories for max scenario, and 26 for refined scenario, as no data available for certain food categories which were therefore not considered in the exposure estimates	–
Concentration data: • use levels considered applicable for all foods within the entire food category, whereas on average, 2.3% of the foods, belonging to food categories with foods labelled with celluloses, was labelled with the additives.	+/–
Maximum level exposure assessment scenario: • authorisation according to Annex III to Regulation (EC) No 1333/2008 not considered • exposure calculations based on the maximum reported use levels from industries	– +

Sources of uncertainties	Direction[a]
Refined exposure assessment scenarios:	
• scenario including only the food categories according to Annex II to Regulation (EC) No 1333/2008	–
• exposure calculations based on the maximum or mean levels (reported use from industries)	+/–
Food supplements consumers only scenario:	
• exposure calculations based on consumers only	+
• exposure calculations based on the maximum levels for food supplements and the mean levels for all other food categories	+/–
• foods which may contain the food additive according to Annex III to Regulation (EC) No 1333/2008 not taken into account	–
FSMP consumers only scenario:	
• exposure calculations based on consumers only	+
• exposure calculations based on the MPL levels for the FSMP and mean levels for all other food categories	+
• foods which may contain the food additive according to Annex III to Regulation (EC) No 1333/2008 not taken into account	–
Uncertainty in possible national differences in use levels of food categories	+/–

(a): +, uncertainty with potential to cause overestimation of exposure; –, uncertainty with potential to cause underestimation of exposure.

Overall, the Panel considered that the uncertainties identified would, in general, result in an overestimation of the real exposure to celluloses (E 460–466, E 468 and E 469) as food additives in European countries considered in the EFSA European database for the maximum level exposure scenario and for the refined scenario, if it was considered that the food additives may not be used in food categories for which no usage data have been provided.

This assumption of non-use was supported by the observation that celluloses (E 460–466, E 468 and E 469) are authorised as Group I food additives in the majority of food categories (Table 13). Since all these food categories correspond to the general Group I food additives authorisation, celluloses (E 460–466, E 468 and E 469) may not necessarily be used in some of these food categories. It may thus be explained why reported use levels adequate for the refined exposure scenario of celluloses (E 460–466, E 468 and E 469) were only available for 26 food categories. The Panel noted that the information from the Mintel GNPD supported the observation that due to its Group I authorisation, celluloses (E 460–466, E 468 and E 469) may not be used in all food categories in which these are authorised (Section 3.3.2). For the 26 food categories considered for the refined exposure assessment, the products labelled with celluloses (E 460–466, E 468 and E 469) were also reported in the Mintel GNPD.

Regarding *food supplements consumers only scenario*, the Panel considered that the uncertainties would result in an overestimation of the exposure to celluloses (E 460–466, E 468 and E 469) as food additives, given that the calculations were based on consumers only of food supplements and assuming a long-term brand loyal consumption of these food products on a daily basis.

Regarding *FSMP consumers only scenario*, the Panel considered that the uncertainties would also result in an overestimation of the exposure, given that the calculations were based on consumers only of FSMP, and no data from industry were provided; therefore, only the MPLs were used.

In none of the exposure scenarios, the use of celluloses (E 460–466, E 468 and E 469) according to Annex III to Regulation (EC) No 1333/2008 was considered. Neglecting this source of exposure may have resulted in an underestimation of exposure to celluloses (E 460–466, E 468–469) in all scenarios.

3.4.2. Exposure via the regular diet

In 2010, the NDA Panel published a scientific opinion on the Dietary Reference Values for carbohydrates and dietary fibre (EFSA NDA Panel, 2010a,b). In this opinion, the intakes of carbohydrates and dietary fibre among several population groups (toddlers, children, adolescents and adults) in EU countries are presented. For adults (19–65 years old), the mean intake for dietary fibre is reported to be in the range from 15.7 to 29.7 g/day. At high levels, the dietary fibre intakes are up to 39 g/day (p95).

Considering that the mean body weight for this population group equals 70 kg (EFSA Scientific Committee, 2012), the highest intake of dietary fibre would be around 560 mg/kg bw per day.

3.4.3. Exposure from all sources

Based on the data from the EFSA NDA opinion on Dietary Reference Values for carbohydrates and dietary fibre (EFSA NDA Panel, 2010a,b), mean intakes of dietary fibre coming from natural sources were estimated in mg/kg bw using default body weight values (EFSA Scientific Committee, 2012). Mean intake from all sources and estimated exposure from food additives (non-brand-loyal scenario) were added in order to give an overall intake estimate of fibre.

Table 17 summarises the estimated exposure to celluloses from their use as food additives and from natural sources.

Table 17: Estimated exposure to celluloses from their use as food additives and from natural sources

	Infants (12 weeks–11 months)	Toddlers (12–35 months)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
Food additive refined exposure, non-brand-loyal scenario (mg/kg bw per day)						
Mean [range]	10 [2-18]	35 [5–64]	35 [11–58]	24 [7–40]	15 [7–23]	11 [7–16]
Natural sources of dietary fibre (EFSA NDA Panel, 2010)						
Mean (g) [range] (g)	NA NA	12 [9.0–15.0]	15 [9.4–20.2]	23 [12.0–33.0]	23 [15.7–29.7]	NA NA
Mean (mg/kg bw)	NA	1008	649	431	311	NA
% of food additives exposure out of all sources						
Mean	–	3%	5%	6%	5%	–

NA, Not available; bw: body weight (default values from EFSA, 2012).

Celluloses intake as food additives would correspond to 6% (non-brand-loyal scenario) of the overall dietary mean intake in the adolescent population.

3.4.4. Exposure via other sources

Exposure to celluloses due to the following uses was not considered in this opinion.

Celluloses as ingredients in foods

Cause and effect relationships have been established between the consumption of hydroxypropyl methylcellulose and a reduction of post-prandial glycaemic responses and maintenance of normal blood cholesterol concentrations. In order to obtain these physiological effects, 4 g of hydroxypropyl methylcellulose per meal or 5 g/day of hydroxypropyl methylcellulose consumed in two or more servings, respectively, are required (EFSA NDA Panel, 2010a,b).

Pharmaceutical uses

Celluloses are used as active ingredients and excipients in medicinal products. As excipients, mostly in medicinal products that come in various types of tablet forms (hard, chewable, film-coated, prolonged-release tablets), in capsules, in granules/powders for oral suspensions, injections, syrups (E 466) and in gels. Their function as excipients is described as disintegrants, diluents/fillers, binders, thickeners, taste maskers, compression aids, stabilising and swelling agents (Guo et al., 1998; Kadajji and Betageri, 2011; Shokri and Adibkia, 2013; Martindale, 2016).

From data provided by the European Medicines Agency (EMA), information about the current medicinal usage of celluloses and their usage as active ingredients and excipients was retrieved (Documentation provided to EFSA n. 11).

In a medicinal product on the European market, methylcellulose is used for the control of consistency of the intestinal content after colostomy, ileostomy and diarrhoea, in the management of diverticular disease and ulcerative colitis, in the management of constipation and as an aid to appetite control and the treatment of obesity. The daily dose used was up to 6 g daily. It was pointed out that

adequate fluid intake should be maintained to avoid intestinal obstruction. Furthermore, it was stated that bulk laxatives such as oral methylcellulose lower the transit time through the gut and could affect the absorption of other drugs. Contraindications are hypersensitivity to methylcellulose, imminent or threatened intestinal obstruction, faecal impaction, difficulties in swallowing, colonic atony, infective bowel disease and severe dehydration. As undesirable effects, gastrointestinal (GI) troubles, including flatulence and abdominal distension, are mentioned [Celevac[17]].

Microcrystalline cellulose (E 460(i)) may also be used in combination with other polymers such as sodium carboxy methyl cellulose (E 466) and guar gum. Incompatibilities of sodium carboxy methyl cellulose (E 466) have been reported with strongly acidic solutions, soluble salts of iron and some other metals, and with xanthan gum (Martindale, 2016).

Upon oral intake of cellulose-containing medicines, reactions noted were abdominal discomfort, abdominal distension/pain, constipation, dysphagia, dyspepsia, weight decrease or increase and flatulence. In addition, in some cases, a chocking sensation was also reported associated to the property of cellulose ethers to swell, forming hydro gels in contact with water (Kamel et al., 2008; FDA, 2015).

4. Biological and toxicological data

4.1. Absorption, distribution, metabolism and excretion

4.1.1. Microcrystalline cellulose (E 460(i)) and powdered cellulose (E 460(ii))

4.1.1.1. Studies on absorption and metabolism of cellulose

JECFA (1998a,b, 1999a,b) and the SCF (1999) referred to several studies on persorption of microcrystalline cellulose particles in animal models. Persorption corresponds to the enteral translocation of particles into the gut-associated lymph system and is one part of the mechanism of absorption of xenobiotics. However, due to the low surface area available for persorption compared to that available for passive diffusion, persorption is generally a minor quantitative contributor to the absorptive capacity of the GI tract. Thus, in cases where persorption is the major, or only, absorption mechanism, only a small amount (a few percent) of the dose can be absorbed.

Animal studies

Microcrystalline cellulose

Four rats received ^{14}C-labelled microcrystalline cellulose at 10% or 20% of the diet (Baker, 1966; cited in JECFA, 1998a,b, 1999a,b). The recovery of radioactivity in faeces ranged from 96% to 104% and was complete for all labelled material. There was no evidence of degradation or digestion and no radioactivity appeared in the urine (only limited information available).

Pahlke and Friedrich (1974) used 29 Wistar rats (14 males and 15 females), 8 mini pigs and 9 Beagle dogs to study the absorption of microcrystalline cellulose (Avicel® PH-101 or Elcema® P 050). The animals were fasted for 12 h prior to oral administration of the test compound in suspension. Rats, dogs and pigs were given 0.5, 140 and 200 g, respectively, of microcrystalline cellulose using whipped cream for preparation of the suspension. In rats, five other vehicles were also used. No details were given about the number of animals used for each experimental trial. The microcrystalline cellulose was stained with Schiff's reagent before application. Venous blood was taken from the animals 1–2 h after administration, haemolysed with saponin and the sediment was examined for particles via light microscopy. The authors reported that small numbers of particles could be detected in venous blood samples by light microscopy, but there were insufficient details to further interpret these findings.

A gavage study in Sprague–Dawley rats used doses of 1,000, 2,000, 3,000, 4,000 and 5,000 mg/kg bw per day microcrystalline cellulose (median particle size 6 μm, 28% of particles < 5 μm) in groups of 5 rats/sex (presumably including control). No absorbed particles were detected in the gut or in the Peyer's patches at 5,000 mg/kg bw per day (no further details; FMC, 1994; cited in SCF, 1999).

In a subchronic gavage study according to current standards, Kotkoskie et al. (1996) examined the possible absorption and translocation of microcrystalline cellulose particles. Groups of 20 male and 20 female Sprague–Dawley rats received once daily via gavage microcrystalline cellulose (median particle size 6 μm, 35% of particles < 5 μm) as a 25% suspension in tap water at dose levels of 0, 500, 2,500 or 5,000 mg/kg bw per day for 90 consecutive days (data on subchronic toxicity are presented in

[17] Celevac, 2016. Product information. https://www.medicines.org.uk/emc/medicine/20700 (accessed January 2016).

Section 4.2.2.1). Necropsy was conducted on study days 91–94 under conditions that reduced the contamination of tissues with particulates, and tissues/organs were processed for histopathology. After conventional histopathology, sections were also examined by polarised light microscopy for the detection of cellulose particles. The limit of detection of birefringent particles was < 1 μm. This specific examination revealed a lack of birefringent cellulose particles in all organs and tissues, including gut-associated lymphoid tissue (GALT), liver, lung and spleen. These results indicated no detectable absorption of particles.

Powdered cellulose

In a feeding study using α-cellulose with Elcema®, a mixture of four types of α-cellulose in the ratio of 1/1/1/1 (particle size 1–50 μm (powder); 1–100 μm (powder); 1–150 μm (fibrillar); 90–250 μm (granulate)) was fed to groups of male and female Wistar rats (number of rats not clearly stated but presumably n = 5/dose per sex) for 30 days at a dietary level of 0% or 50% (equivalent to 45,000 mg/kg bw per day) (Ferch, 1973a,b). Statistical analysis of results was not performed. All rats were subjected to a 'persorption test': on the last day of the treatment period a cellulose-staining dye (substitution of 5% of Elcema® by Remalbordo®) was added to the diet. The animals were sacrificed 24 h after addition of the dye, followed by histological examination of the GI tract, spleen, liver, kidney and heart for stained particles. Even at this high dose level, no detectable absorption of cellulose particles occurred.

Human studies

Microcrystalline cellulose

The absorption of ingested radiolabelled microcrystalline cellulose was examined in one male volunteer (no further details reported) (Baker, 1968; referred to by JECFA, 1998a,b, 1999a,b). In a 15-day adaptation period, the subject received 150 g/day of unlabelled microcrystalline cellulose in two portions. He then received 47.6 μCi of ^{14}C-labelled microcrystalline cellulose in two portions on one day. The following 10 days the supplementation of the diet with unlabelled microcrystalline cellulose was continued. After oral exposure to the labelled test substance, samples of faeces and urine collected over 24 h were examined for radioactivity. All administered radioactivity (98.9 ± 3.0%) was recovered from the faeces within 2 days and no radioactivity appeared in the urine or in the expired CO_2, suggesting no absorption of microcrystalline cellulose from the GI tract.

In another publication (Pahlke and Friedrich, 1975), the authors reported data on absorption of microcrystalline cellulose (no further details about the test item) in humans. The study was performed in one male volunteer. Due to the insufficient reporting, the Panel considered this study as not relevant for risk assessment.

4.1.1.2. Studies on fermentation of cellulose

There is evidence that certain high molecular weight dietary polysaccharides can be partially broken down by fermentation in the large intestine of animals and man. However, celluloses are known to be less fermentable than other polysaccharides such as gums, starches or pectins. In addition to intermediate metabolites such as lactic, acrylic or fumaric acids, the main end products of this colonic anaerobic digestive process are short-chain fatty acids (SCFA) such as acetic, propionic and butyric acids, which are absorbed from the colon (Cummings and Englyst, 1987).

In vitro studies

Microcrystalline cellulose

The fibrolytic microbiota of the human large intestine was examined to determine the numbers and types of cellulolytic and hemicellulolytic bacteria present (Wedekind et al., 1988). Faecal samples from each of five individuals contained bacteria capable of degrading the hydrated cellulose in spinach and in wheat straw pretreated with alkaline hydrogen peroxide (AHP-WS), whereas degradation of the relatively crystalline cellulose in Whatman no. 1 filter paper (PMC) was detected for only one of the five samples. The mean concentration of cellulolytic bacteria, estimated with AHP-WS as a substrate, was 1.2×10^8/mL of faeces. Pure cultures of bacteria isolated on AHP-WS were able to degrade PMC, indicating that interactions with other microbes were primarily responsible for previous low success rates in detecting faecal cellulolytic bacteria with PMC as a substrate. The cellulolytic bacteria included *Ruminococcus* spp., *Clostridium* sp. and two unidentified strains. According to the authors, this work

demonstrated that many humans harbour intestinal cellulolytic bacteria and that a hydrated cellulose source such as AHP-WS is necessary for their consistent detection and isolation.

Microorganisms involved in the breakdown of cellulose were isolated, quantified and identified from human faecal samples (n = 34) (Robert and Bernalier-Donadille, 2003). The cellulolytic isolates corresponded to new *Ruminococcus* species and to *Enterococcus* species. These isolated species were incubated for 10 days at 37°C with 100 mg of paper cellulose as sole energy source. The end products of cellulose fermentation were mainly succinic acid, acetic acid and ethanol. The authors stated that microcrystalline cellulose degraders could only be enumerated in faecal samples from methane excretors, indicating that these species seem to be linked to methanogenic archaea in the gut.

In further investigations, the composition and activity of the cellulose-degrading bacterial population were shown to vary depending on the presence or absence of methanogens in the human gut (Chassard et al., 2010). The main microcrystalline cellulose-degrading bacteria belonged essentially to *Bacteroidetes* in non-methane-excreting subjects, while they were predominantly represented by *Firmicutes* in methane-excreting individuals. The degradation of cellulose has been shown *in vitro*.

In additional experiments, an anaerobic cellulolytic bacterial strain (*Ruminococcus champanellensis* sp. nov., strain designated 18P13(T)) was isolated from a human faecal sample (Chassard et al., 2012). In *in vitro* experiments, this strain was able to degrade microcrystalline cellulose (Avicel® PH-101), but the utilisation of soluble sugars was restricted to cellobiose. Acetic and succinic acid were the major end products of cellulose and cellobiose fermentation.

Powdered cellulose

Sunvold et al. (1995) evaluated the influence of GI tract microflora from several species on fibre fermentation characteristics *in vitro*. Among other fibrous substrates (beet pulp, citrus pulp and citrus pectin), powdered cellulose (Solka Floc) was incubated for 6, 12, 24, and 48 h with ruminal fluid from cattle or faeces from dogs, cats, pigs, horses or humans. In the case of human faeces, after pooling data across all substrates and fermentation times, organic matter (OM) disappearance was 41.2% and acetic, propionic, butyric acid and total SCFA production were, respectively, 1.70, 0.60, 0.39, and 2.70 mmol/g of OM. Lactic acid production was 0.06 mmol/g of OM. When data were pooled across species, substrate OM disappearance and SCFA production ranked from least to greatest in the following order: cellulose < beet pulp < citrus pulp < citrus pectin. According to the authors, the fermentation of different fibrous substrates by faecal or ruminal microflora from various species seems to be dependent not only on the fermentative activity of the microbial population but on other factors such as lag time and rate of digesta passage.

In vivo *study*

Microcrystalline cellulose

In rat studies, evidence of fermentation of microcrystalline cellulose by the microflora of the large intestine was shown. Male Wistar rats (n = 6 per group) were exposed via the diet (adapted from the AIN-76A purified diet; fibre-free) at a level of 5% microcrystalline cellulose (Avicel® PH-101, unlabelled test substance) for 14 days (Hsu and Penner, 1989). Food consumption was analysed, as well as cellulose content in faeces (validated methods). The mean total ingestion of microcrystalline cellulose was 13.1 g/rat and the mean faecal output 11.9 g/rat, resulting in a mean digestibility of 9%. The individual digestibility ranged between 6.4% and 10.8%. The authors stated that this variation may reflect differences in the population of cellulolytic bacteria in the intestine of individual rats.

The fermentation of cellulose was also studied in a comparative study conducted in conventional or germ-free (absence of intestinal microflora) male Wistar rats (Juhr and Franke, 1992). In this study, ^{14}C-labelled starch-free cellulose (synthesised by fermentation of [U-^{14}C]glucose with *Acetobacter xylinum*, was used. No data were given about the form of the test item or further impurities. Groups of 5 rats received a single oral application of 145 kBq of the labelled cellulose in 0.5 mL of physiological saline by gavage (no further details about the dose). Excretion via faeces, urine and exhaled air was measured for 30 h in metabolism cages. The total recovery after 30 h was 101% in both groups, illustrating the validity of the methods. In germ-free rats, 94.6% of the applied radioactivity was detected in the faeces and intestinal content, 4.6% in the carcass, 1.1% in exhaled air (CO_2 measured) and 0.7% in urine. In conventional rats, however, 65.4% of the applied radioactivity was found in the faeces and intestinal content, but 30.0% in exhaled air, 3.9% in the carcass and 1.6% in urine. The authors stated that the portion of the dose remaining within the intestine at 30 h was resistant to fermentation. In germ-free rats, in the absence of fermentation of cellulose via the

intestinal microflora, nearly complete excretion via faeces was demonstrated (94.6%), suggesting no or little absorption from the GI tract. However, the absorption rate of 6.4% (4.6% in the carcass, 1.1% in exhaled air and 0.7% in urine) was clearly above background and may represent persorption and/or metabolism of radiolabelled impurities of the test item. Fermentation of cellulose is unlikely because the germ-free status of the rats was verified before and after the treatment. There is evidence from experiments with conventional rats that fermentation of cellulose occurs and the fermentation products (not identified or specified) were absorbed and mainly used as energy source, since 30% of the applied radioactivity was exhaled via $^{14}CO_2$.

4.1.1.3. Studies on excretion of cellulose in humans

Most of the excretion studies performed in humans used celluloses prepared from botanicals which were, generally, not specified.

Unspecified cellulose

Southgate and Durnin (1970) compared the intake and the faecal excretion of proteins, fat, pentosan and cellulose (origin unspecified) in young (n = 26) and elderly (n = 23) volunteers of both sexes. The authors reported that the apparent digestibility of orally administered cellulose in the human gut ranged from 15% to 26% and from 26% to 55% in young and elderly subjects, respectively.

Kelleher et al. (1984) used ^{14}C-labelled cellulose prepared from *Cana indica* leaves, which were allowed to photosynthesise in an atmosphere of $^{14}CO_2$ for 24 h. The test item contained also labelled starch. The purification of the commercial product resulted in a ^{14}C-cellulose in which > 90% of the starch had been removed. Less than 1% of the test substance was soluble in water and 98% was retained by a 0.45 μm Millipore filter. The experiment was performed in 10 volunteers (6 elderly and 4 younger subjects without GI disease). All fasted subjects received orally 500 mg ^{14}C-labelled cellulose mixed with 15 g mashed potatoes, followed by a cup of tea. Thereafter, the volunteers consumed mixed normal diets. Excretion of the applied radioactivity was determined by liquid scintillation measurements of faeces (n = 9) and exhaled air (n = 8; 4 elderly and 4 younger volunteers). The faecal collection was nearly complete and reached a mean of 92% in nine subjects (one subject excluded from faecal results). A mean of 57% of the applied radioactivity was excreted in the faeces (no data about sampling period) and 16% of applied radioactivity was expired as $^{14}CO_2$ (collection time 72 h); an average of 7.5% of the faecal radioactivity was water-soluble. About 4% of the administered radioactivity appeared in the exhaled air 0–10 h after ingestion. In the four elderly subjects, a mean of 18% of the applied dose occurred in expired air 10–72 h after application, but only 7% in the four younger volunteers. The early exhalation of $^{14}CO_2$ was discussed by the authors as due to possible metabolic products of impurities (non-cellulose polysaccharides). Metabolites in faeces were not analysed. The authors concluded that a significant quantity of ingested cellulose was metabolised within the human GI tract, absorbed and appeared in the expired air as $^{14}CO_2$.

Walters et al. (1989) used the same purified test item in additional *in vitro* experiments for specifying that the purified ^{14}C-labelled cellulose was completely hydrolysed by cellulase. In a first trial, six healthy volunteers (40–50 years of age, no further details) received 500 mg of the radiolabelled cellulose after an overnight fast. The exhaled radioactivity was measured 0–24 h after ingestion (no data about other excretion routes); 1.6% of the applied dose was exhaled during the first 4 h, whereas the cumulative amount of exhaled $^{14}CO_2$ reached 11% of the applied radioactivity. In a second trial, the degradation of the purified ^{14}C-labelled cellulose was compared in six subjects with an ileostomy, following total colectomy and rectal resection. Using the same experimental protocol, 1.1% of the applied radioactivity was exhaled within the first 4 h after ingestion, but the cumulative amount in expired air (0–24 h) was only 3% in the ileostomy subjects; negligible $^{14}CO_2$ excretion was detected from 15 h onwards. Analysis of ileostomy contents showed that 81% of the administered cellulose was excreted by this route. According to the authors, this comparison of normal and ileostomy subjects revealed the important role of the colonic microflora in the degradation of cellulose in the human GI tract. In a third trial, increase (by 54%) in exhaled $^{14}CO_2$ was observed in four healthy volunteers, pretreated with increased dietary fibre for 3 months.

Powdered cellulose

The fate of orally ingested ^{131}I-labelled α-cellulose was quantified in eight healthy volunteers (four men, aged 27–75 years; four women, aged 21–76 years) by monitoring samples of faeces, urine and blood (Carryer et al., 1982). Details about the test substance were not available, except for the statement that strands < 1 mm were eliminated by sieving before use. The volunteers ingested

100 μCi of the radiolabelled cellulose with a meal after an overnight fast. Complete urine and stool collections were obtained over a 5-day period after ingestion; in two subjects, faeces were also collected at days 6 and 7 and analysed. Venous blood samples were taken once daily. Aliquot samples of faeces and urine were filtered (0.45 μm Millipore filter) to assess also the unbound radiolabel. No radioactivity was detected in blood, but 87% of the applied dose was excreted via faeces (58% at days 1 and 2) and 2% via urine (1.6% at days 1 and 2). Less than 2% of radioactivity in faeces, but total radioiodine in urine, was unbound. The total recovery of the applied radioactivity was 89%; the authors did not discuss the fate of the remaining amount, but concluded that ^{131}I-labelled α-cellulose was resistant to degradation by colonic microflora due to the large fibre size and/or chemical transformation of the test item produced by the radioactive labelling.

4.1.2. Methyl cellulose (MC; E 461)

Animal data

Groups of adult male Hooded Wistar rats were fed sucrose-based diets containing 80 g/kg of MC of low (25 cP), medium (400 cP) and high (1,500 cP) viscosity (Topping et al., 1988). After 10 days of adaptation to the three diets, blood and liver were sampled. The whole caeca were also removed and the contents extruded for measurement of weight, viscosity, pH, volatile fatty acids (VFA) and bile acids. The viscosity of stomach and caecal contents was increased in proportion to that of the dietary fibre. Plasma cholesterol and VFA concentrations were unaffected by the viscosity of the dietary fibre. The concentrations of acetic and propionic acid in caecal contents decreased with increasing viscosity of the diet; according to the authors, this effect could be related to the availability of dietary starch and sucrose trapped in the methyl cellulose matrix. Finally, this study gave no indication of fermentation of MC by gut microflora.

Male and female Sprague–Dawley rats (3/sex per group, 185–250 g) were dosed once or once daily over 5 days via gavage with ~ 500 mg/kg bw per day of ^{14}C-MC labelled in the methoxyl group and with a viscosity of 3,300 cP (Braun et al., 1974). In the single-dose study, the animals were kept in metabolism cages for separate collection of urine, faeces and CO_2 in expired air. Urine and faecal samples were collected at 6-h intervals for the first 24 h and at 12-h intervals thereafter. The rats were killed 4 days after dosing, the carcasses were skinned and the hearts, livers, lungs, kidneys and GI tracts were removed. In the repeated-dose study, rats were housed in metabolism cages designed for a separate collection of urine and faeces. Samples of excreta were collected at 24-h intervals, the rats were killed 24 h after the final dose, and the carcasses and tissue samples were assayed for radioactivity contents. In the single-dose study, 96–105% of the total dose of ^{14}C activity was eliminated via the faeces within 48 h. No radioactivity was detected in the expired air and less than 0.1% of the dose was found in the urine, selected tissues and remaining carcass. In the repeated-dose study, there was also no increase in the ^{14}C activity in the heart, kidney, liver, lung, carcass and skin, as the total amount found in these tissues was less than 0.1% of the total dose. The Panel noted that all the administered MC was eliminated in the faeces of the rats and was neither absorbed intact, nor fermented, in the GI tract.

Human data

In an older study (Machle et al., 1944) with two male adults and one 10-year-old girl, it was shown that nearly the entire MC (up to > 95%) was excreted via faeces, practically unaltered, within 3 days. In each experiment, 10 g of MC were given orally in a single dose, except in one experiment, where 5 g were given. The product was taken as a 5% solution and in one experiment as a gel. Irrespective of the accompanying diet (e.g. milk diet, customary diet, bran daily), practically all of the methoxyl groups of ingested MC were recovered from the faeces.

4.1.3. Ethyl cellulose (EC; E 462)

No data available.

4.1.4. Hydroxypropyl cellulose (HPC; E 463)

Animal data

Male and female Wistar-Imamichi strain rats (3/sex per group) were dosed once via gavage with 1,300 mg/kg bw of ^{14}C-HPC (labelling in the methylenic carbon of the hydroxypropyl group),

containing 12% of the hydroxypropyl group (2.74 μCi/mg) (Kitagawa et al., 1976a). After dosing, the rats were placed in metabolism cages and urine and faeces were collected for 96 h. For the detection of possible metabolites in urine, gel filtration was used. Bile duct was cannulated and samples were taken for 24 h and at different time points (6, 12, 24, 48 and 72 h after dosing). Radioactivity was determined in tissues and GI contents (blood, liver, kidney, lung, heart, spleen, cerebrum, cerebellum, thymus, thyroid, fat, stomach and intestinal contents from the upper part of the duodenum to the caecum, testes, prostate, uterus, ovaries). Up to 69% and 97% of the radioactivity were excreted in the faeces within 24 and 96 h, respectively. Only minor amounts (up to 2.6%) were excreted in urine within 96 h. Less than 0.015% was excreted in bile within 24 h after dosing. Due to the very minor amounts of ^{14}C-HPC excreted via urine, no specific metabolites could be identified. Their molecular weight was slightly higher than that of glycerol or glucose and the elution position was different from propylene glycol, which was present at a level of < 2% in the test material. Apart from liver and kidneys, radioactivity was not detectable in other tissues examined. Peak amounts in livers were given with 1.02% of the dose in male rats 12 h after dosing, and with 0.026% of the dose in females, 24 h after dosing.

When 250 or 1,000 mg/kg bw of ^{14}C-HPC were administered to rats in a 5% aqueous solution, radioactivity no greater than 0.01% of the administered dose was detected in organs, urine and expired air (Industrial Bio-Test Lab, 1964; unpublished report, cited in JECFA, 1990). Recovery of activity in the faeces varied from 98.3% to 102.7%. Hence, orally ingested material was not absorbed from the GI tract of the rat and was excreted quantitatively in the faeces, principally in the first 48 h. To check on enterohepatic circulation, two additional rats with cannulated bile ducts were administered 1,000 mg/kg bw of radiolabelled material. Bile was collected for 72 h, but no significant activity was found.

4.1.5. Hydroxypropyl methyl cellulose (HPMC; E 464)

Experimental data

In vitro

Wyatt et al. (1988) compared the effect of a fibre-free diet and of diets containing non-digestible polysaccharides, including HPMC, on rat caecal and colonic physiology and microflora. All polysaccharide-containing diets led to enlargement of the caecum and colon, associated with increased weight of contents and tissue. *In vitro*, HPMC remained almost completely unfermented, with only 5% of the substrate utilised after 7 days of incubation. According to the authors, caecal and colonic enlargement would be due to tissue hypertrophy in response to increased bulk of contents, irrespective of the nature of that bulk, which varies with diet. It would be unlikely that SCFA or other microbial metabolites are the stimulus for the trophic response seen when non-digestible dietary polysaccharides are fed to rats.

In vivo

Groups of three young male and three young female Sprague–Dawley rats were dosed with 500 mg/kg bw per day of ^{14}C-HPMC (viscosity of 2.25 cP) once or once daily over five consecutive days via gavage (Gorzinski et al., 1986). After single dosing, about 73–101% of the applied dose was excreted within 24 h via faeces (100–105% within 72 h), while within 72 h only up to 1.5% was found in urine, 0.2% in carcass and tissues and 0.07% in expired air. In bile, a collection over 24 h in two male rats gave 0.05% of the applied dose. In plasma, the elimination of radioactivity was monophasic, with a half-live of about 2 h. Most of the residual radioactivity was found in the GI tract (no details given). In urine, methyl ethers of glucose and oligomers were identified, determined by thin layer chromatography in 6-h urine from one animal of each sex. Also, after dosing once daily over 5 days, most of the applied dose was excreted via faeces (97–104%), while only 1% was recovered in urine. There was no evidence of accumulation in the tissues examined (adrenals, brain, heart, liver, kidneys and spleen). A determination in exhaled air was not performed.

Human data

In a study with 25 young and healthy adults (23 males and 2 females), each person was given 3 graduated doses of HPMC ranging from 0.6 to 8.9 g (Knight et al., 1952). The time interval between the doses was at least 1 week. Following each dose, stool specimens were collected at approximately 24-h intervals for 72 or 96 h. For a determination of the quantitative amounts of HPMC in the samples of dried faeces, an analytical procedure, consisting of a methoxyl determination made directly on the

faeces samples, was used. Nearly all of the ingested substance (average of total recovery 97%, with a range of 89–110%) was excreted via faeces within 96 h following administration.

4.1.6. Ethyl methyl cellulose (EMC; E 465)

Animal data

After feeding a single dose of 600 mg of EMC in the diet of rats, about 90% of the dose was recovered from the faeces by the end of the fourth day (Gage, 1962; unpublished report, as cited in JECFA, 1990). Nearly all alkoxyl groups remained attached to the cellulose chain during passage through the gut.

4.1.7. Sodium carboxy methyl cellulose (NaCMC; E 466)

Experimental data

Wyatt et al. (1988) compared the effect of a fibre-free diet and of diets containing non-digestible polysaccharides, including CMC, on rat caecal and colonic physiology and microflora. All polysaccharide-containing diets led to enlargement of the caecum and colon, associated with increased weight of contents and tissue. CMC had the most marked effect and treated animals had watery faeces. *In vitro*, CMC was poorly fermented even after prolonged incubation. According to the authors, caecal and colonic enlargement would be due to tissue hypertrophy in response to increased bulk of contents, irrespective of the nature of that bulk, which varies with diet. It would be unlikely that SCFA or other microbial metabolites are the stimulus for the trophic response seen when non-digestible dietary polysaccharides are fed to rats.

Adiotomre et al. (1990) investigated the effects of dietary fibres, including NaCMC, on caecal fermentations by using fresh human microflora. Evolution of SCFA and water-holding capacity after fermentation were also measured. Among other polysaccharides, NaCMC (E 466 grade) yielded low amount of total SCFA (25.8 vs 15.5 mmol/L for controls). The major SCFA produced were acetic and propionic acids, with smaller amounts of butyric, isobutyric, valeric and isovaleric acids. By contrast, the amount of water held by 1 g of the fermented residue was the highest in the case of NaCMC (11.9 vs 0.91 g/g for controls).

The absorption and excretion of NaCMC was examined in rats (Bär et al., 1995b). The ^{14}C label was in the two carbon atoms of the carboxymethyl group and the specific radioactivity was 0.27 μCi/mg. One group of four male and four female Wistar rats were fed diets with 5% unlabelled CMC for a 2-week adaption period, followed by a single oral dose of 500 mg/kg bw of a ^{14}C-CMC solution via gavage. Immediately after dosing, the rats were housed for 48 h in metabolism cages and then for 72 h in open metabolism cages. Expired CO_2 was collected every 2 h during the first 24 h and then at 12-h intervals until 48 h. Urine and faeces were collected. At study termination on day 5, the animals were killed and plasma and blood cells were collected. The content of the GI segments, testes, prostate, uterus, ovaries, adrenals, urinary bladder, as well as samples of perirenal fat, abdominal skin and skeletal muscle, together with the remaining carcass were collected and weighed. The ^{14}C administered and recovered in excreta and different organ and tissue samples was determined by liquid scintillation counting. At the end of the 5-day sampling period, the total mean recovery rate for ^{14}C-CMC was 98.07% and the applied dose was mainly excreted via faeces (94.39%). Most of the radioactivity was excreted within 48 h after dosing. In the contents of the GI tract, only about 0.01% of the dose was recovered. Only small amounts were excreted via urine (less than 2% of the dose). Via expired CO_2, only < 1% of the applied radioactivity was expired within 48 h. The highest expiration rate was seen during the first 2 h after dosing (0.19%). Only a small incorporation of the ^{14}C label in organs and tissues was seen (0.58%), with highest amounts found in fat, skin, muscles and liver. An examination of the pooled faeces showed that about 51% of the label from ^{14}C-CMC remained with the sediment obtained by centrifugation of the faecal suspensions. As most of the soluble ^{14}C-labelled excretion products were extracted in a first extraction step (the second step provided only about 10% of the radioactivity of the first step), the label was apparently tightly bound to the faecal matrix or was incorporated in the bacterial cells. Gel permeation chromatography (GPC) of the dosing solutions and the faecal extracts revealed that CMC was depolymerised during intestinal passage.

In an unpublished study (Wiebe, 1962; cited in JECFA, 1990), ^{14}C-labelled CMC containing up to 0.34% radioactive sodium glycolate was given orally to two groups of five male rats each, in a dose of 400 mg. No detectable activity (less than 0.02% of the dose) was found in the livers and kidneys and

about 0.14% of the administered radioactivity was found in the 48-h urine samples. This amount, however, could be accounted for the free radioactive glycolate present in the test compound.

Five rats (strain and sex not specified) were fed 5 g of CMC collectively and faeces were collected at 24-h intervals. Approximately 90% of the applied dose was recovered in the faeces (Shelanski and Clark, 1948; as cited in JECFA, 1990).

In a study with six young albino rats, CMC was given via diet at levels of 5, 10 or 14% during four periods of 10 days each. About 96.3–100% of the applied doses could be recovered in faeces (Ziegelmayer et al., 1951).

In a study with three rabbits, CMC was given via diet at levels of 4.76% and 9.09% during two periods of 10 days each. About 48–57% of the applied doses could be recovered in faeces (Ziegelmayer et al., 1951).

Human data

In three volunteers given daily oral doses of 20 or 30 g of CMC over 4 days, about 90% of the applied doses could be recovered in faeces. The dosing was well tolerated (Ziegelmayer et al., 1951).

4.1.8. Cross-linked sodium carboxy methyl cellulose (E 468)

As reported above, a comparative disposition study was carried out with ^{14}C-labelled sodium CMC and enzymatically hydrolysed sodium CMC in adult Wistar rats (8 animals/sex; age not stated) (Bär et al., 1995b). The enzymatically hydrolysed sodium CMC was recovered from the GI tract with an unchanged molecular weight, whereas the sodium CMC was reduced in molecular size. This implies that the passage of CMC through the rat GI tract leads to the breakdown of some of the monomers of CMC to units similar to the ones of its enzymatically hydrolysed counterpart. JECFA (2003) noted that the cross-linked form will be more insoluble in water and therefore less likely to be absorbed and degraded than the parent compound itself.

4.1.9. Enzymatically hydrolysed carboxy methyl cellulose (E 469)

The absorption and excretion of partially enzyme-hydrolysed ^{14}C-labelled enzymatically hydrolysed carboxy methyl cellulose was compared in rats to those of CMC in the above described study (Bär et al., 1995b). Following the same experimental protocol, most of the radioactivity (89–99% of the dose) was excreted within 48 h after dosing. In the contents of the GI tract, at study termination, only about 0.01% of the dose could be recovered. Only small amounts (about 2%) were excreted via urine. Via expired CO_2, only < 1% was expired within 48 h. Only a small incorporation of the ^{14}C label in organs and tissues was seen (0.75%), with highest amounts in fat, skin, muscles and liver. An examination of the pooled faeces showed that about 35% of the label from ^{14}C-enzymatically hydrolysed carboxy methyl cellulose remained with the sediment obtained by centrifugation of the faecal suspensions. The label was apparently tightly bound to the faecal matrix or was incorporated in the bacterial cells. GPC of the dosing solutions and the faecal extracts revealed that enzymatically hydrolysed carboxy methyl cellulose was excreted nearly intact.

4.1.10. Summary

Animal and human data clearly demonstrated that microcrystalline and powdered cellulose are not absorbed intact in the GI tract and could be fermented during their passage through the large intestine by strains of bacteria found in the human colon. Microcrystalline, powdered and modified celluloses would be less fermented than other polysaccharides such as gums, starches or pectins. A comparative human study in normal and ileostomy subjects confirmed the role of the intestinal microbiota in the degradation of ^{14}C-labelled cellulose in the human GI tract. Data on methyl cellulose (E 461), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464), ethyl methyl cellulose (E 465), sodium carboxy methyl cellulose (E 466), cross-linked sodium carboxy methyl cellulose (E 468) and enzymatically hydrolysed carboxy methyl cellulose (E 469) demonstrated that these modified celluloses would not be absorbed intact and not fermented in the GI tract of animals or humans. They are excreted intact mainly via faeces (more than 90% of the administrated doses), while only minor amounts of radiolabelled material are excreted via urine or via expired air (as $^{14}CO_2$) and there is no indication for accumulation in the body. Overall, by comparing their respective databases, the Panel considered that microcrystalline, powdered and modified celluloses would not be absorbed intact and would be less fermented than other polysaccharides such as gums, starches or pectins.

4.2. Toxicological data

Specific toxicity data were not available for all the celluloses for all endpoints. Where studies were conducted, the specifications of the celluloses tested were not always clearly stated. However, given their structural, physicochemical and biological similarities, the Panel considered it possible to read-across between all the celluloses.

4.2.1. Acute oral toxicity (E 460(i), E 460(ii), E 462–464, E 466)

Data on acute oral toxicity were available for microcrystalline cellulose, powdered cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose and sodium carboxy methyl cellulose. Apart from one unpublished study with hydroxypropyl methyl cellulose, where an oral LD_{50} value of > 1,000 mg/kg bw was given for rats (CTFA, 1978), the oral LD_{50} values for the different other celluloses were consistently ≥ 3,000 mg/kg bw (Documentation provided to EFSA n. 20, 25, Freeman, 1996a; referred to by JECFA, 1998a,b, 1999a,b, Palotta, 1959; referred to by JECFA, 1998a,b, 1999a, b, Rowe et al., 1943; Shelanski and Clark, 1948; Industrial Bio-Test Lab, 1962; Kitagawa et al., 1970, 1976b; Moreno, 1977). Therefore, the Panel considered the oral acute toxicity of these compounds to be low.

4.2.2. Short-term and subchronic toxicity

4.2.2.1. Microcrystalline cellulose (E 460(i))

Male Wistar rats (n = 6/group) fed a diet containing 5% microcrystalline cellulose (Avicel® PH-101; equivalent to 6,000 mg/kg bw per day) for 14 days did not show any effects on body weight gain, final body weight or food consumption in comparison to the controls receiving fibre-free diet (Hsu and Penner, 1989). The treatment induced a significant increase in wet and dry weight of faeces; the cellulose content of faeces reached 70%.

A subacute 28-day gavage study in Sprague–Dawley rats used doses of 1,000, 2,000, 3,000, 4,000 or 5,000 mg Avicel® FD-006/kg bw per day microcrystalline cellulose (median particle size of 6 μm; 28% of particles with size < 5 μm) in groups of five rats/sex (presumably including control) (FMC 1994, referred to by SCF, 1999). No adverse toxicological effects occurred at any dose level. No persorbed particles were detected in the gut or in the Peyers' patches at 5,000 mg/kg bw per day. The Panel noted that the test substance was not compliant with the specifications of the food additive.

Male Wistar rats (n = 12 per group) were fed for 4 weeks a diet (26% casein) supplemented with 0%, 5%, 10% or 20% microcrystalline cellulose (Avicel®) (equivalent to 0, 2,500, 5,000 or 10,000 mg/kg bw per day) (Sundaravalli et al., 1971). Rats were sacrificed and the body composition was analysed (moisture, fat and protein). No effects were detected. The body weight gain was not significantly influenced. In additional experiments, groups of 12 male Wistar rats received for 5 weeks a cholesterol-rich diet (1.5% cholesterol) supplemented with 0% or 20% microcrystalline cellulose. Cellulose treatment reduced significantly the total cholesterol level in plasma and liver and increased the excretion of bile acids in the faeces.

Groups of five male rats (no data about strain) received 0.5% or 10% microcrystalline cellulose (equivalent to 450 or 9,000 mg/kg bw per day) in their diet for 8 weeks (Asahi Chemical Industry Co., 1966; referred to by JECFA, 1998a,b, 1999a,b). The high-dose group showed slightly lower body weights than control rats. Haematology, serum chemistry and vitamin B1 levels in blood and faeces revealed no differences from control (no further details available).

In a study in Russian (Dorkina et al., 2007), groups of six male and six female Wistar rats received 0, 200, 1,000 or 2,000 mg microcrystalline cellulose/kg bw per day (dosing not clearly stated, presumably by gavage and in mg/kg bw per day) for 2 months. The treatment reduced significantly the body weight gain in males and females at ≥ 1,000 mg/kg bw per day, and in females also at the low dose level. However, the initial weight at the start of the experiment differed between groups (difference > 10%), limiting the evaluation of this result. Haematology revealed statistically significant effects even at the low dose level for some parameters (e.g. thrombocytopenia, erythrocytopenia, decreased haematocrit, reticulocytosis, reduced number of monocytes but increased number of lymphocytes and segmented neutrophils, decreased coagulation time). However, no data were given on the historical range of these parameters. The toxicological relevance of these effects is questionable and not in accordance with other studies.

Sprague–Dawley rats (20/sex per group) received a diet containing 0%, 5% or 10% microcrystalline cellulose (Avicel® PH-101; median particle size 70 μm) (equivalent to 0, 4,500 or 9,000 mg/kg bw per day) for 13 weeks (Schmitt et al., 1991). Animals were observed daily for overt signs of toxicity. Body weights and food consumption were determined weekly for all animals. Haematology and clinical chemistry analyses were performed at termination (n = 10/group). Liver, adrenals, testes with epididymides, and kidney weights were recorded for all animals. All animals were necropsied and tissues from control and high-dose animals, as well as all gross lesions from all animals, were examined microscopically (no further data). No treatment-related clinical signs or effects on mean body weight or mean body weight gain were noted. The food consumption was increased in treated groups due to the reduced caloric intake. In haematology and clinical chemistry, no treatment-related effects were detected. There were no notable gross pathologic findings at necropsy and no effects on organ weights. Microscopic evaluation of tissues revealed no treatment-related lesions, including in the GI tract. The Panel considered 10% microcrystalline cellulose in the diet (9,000 mg/kg bw per day, the highest dose tested) as the no observed adverse effect level (NOAEL). Similar results were obtained with cellulose fibre (Cellulon™; cellulose produced by a bacterial fermentation process) using the same experimental design and dose levels (Schmitt et al., 1991).

Groups of 20 male and 20 female Crl:CD(R) BR/VAF/Plus rats received a diet containing 0 (control), 25,000 or 50,000 mg Avicel® RCN-15/kg diet (a mixture of 85% microcrystalline cellulose with 15% guar gum) (equal to 1,794 or 3,769 mg/kg bw per day for males and 2,131 or 4,446 mg/kg bw per day for females) for 90 days (Freeman, 1992a referred to by JECFA 1998). The study was performed according to the current guidelines. During the study, no treatment-related clinical signs were noted. In the high-dose group, increased food consumption was observed during several weeks, probably due to the increased dietary fibre content. This effect was also observed during the first week in the 25,000 mg/kg group. However, body weight gain was not affected. No treatment-related effects were detected in clinical chemistry and haematology. Necropsy revealed no evidence of treatment-related changes. The organ weights were unaffected by the treatment. Histopathology was performed in 34 organs or tissues, including the GI tract and GALT of the ileum; there was no evidence for toxicity of microcrystalline cellulose (data from secondary source). The author noted that the NOAEL was 50,000 mg/kg diet, the highest dose tested, (equal to 3,769 mg/kg bw per day for males and 4,446 mg/kg bw per day for females). The Panel agreed with this NOAEL.

In a 90-day study performed according to the current guidelines, Sprague–Dawley rats (20/sex per group) received a diet containing 0 (control), 25,000 or 50,000 mg Avicel®CL-611/kg diet (microcrystalline cellulose and carboxy methyl cellulose) (equivalent to 0, 2,250 or 4,500 mg/kg bw per day), Documentation provided to EFSA n. 32). Clinical signs were recorded daily. Body weights and food consumption were measured weekly. Blood samples were collected at termination for haematology and clinical chemistry. Necropsy was conducted on study days 91–94 and organ weights (brain, liver, kidneys, adrenals and testes) measured. Thirty-three organs/tissues of high-dose and control rats were examined histopathologically. No treatment-related clinical signs and no mortality occurred. In males, no effect on body weight and body weight gain was observed. Males of both treated groups showed increased food consumption. This effect was considered to be a response to the decreased caloric content of the test diets. Females of both treated groups showed a decreased body weight and body weight gain, without any significant increase in food consumption. The effect on body weight gain was considered to be caused by the decreased caloric intake. There were no other toxicologically relevant effects in treated animals with respect to clinical chemistry, haematology and absolute and relative organ weights. No treatment-related lesions were detected in histopathology. The authors considered the high-dose group (4,500 mg/kg bw per day) as the NOAEL of this study. The Panel agreed with this NOAEL.

A subchronic gavage study was conducted according to current standards to evaluate the potential toxicological effects associated with intestinal translocation of microcrystalline cellulose (Kotkoskie et al., 1996). Sprague–Dawley rats (20/sex per group) received once daily, via gavage, microcrystalline cellulose (Avicel® FD-006, median particle size 6 μm, 35% particles < 5 μm) for 90 consecutive days as a 25% (weight/volume preparation) suspension in tap water at dose levels of 0, 500, 2,500 or 5,000 mg/kg bw per day. The suspension was prepared fresh daily. The control group received the same dosage volume of tap water as the high-dose group. Clinical signs were recorded daily after dosing. Body weights and food consumption were measured weekly. Blood samples were collected at termination for haematology and clinical chemistry. Necropsy was conducted on study days 91–94 and the organ weights (brain, liver, kidneys, adrenals and testes) measured. Thirty three organs/tissues of high-dose and control rats were examined histopathologically. After conventional histopathology,

sections were also examined by polarised light microscopy for the detection of cellulose particles (limit of detection of birefringent particles < 1 μm). No treatment-related mortality occurred. The only treatment-related clinical sign noted during the study was pale faeces at ≥ 2,500 mg/kg bw per day. This effect was attributed to the presence of the test material in the faeces and was not considered by the authors to be of toxicological relevance. Body weights or body weight gains were not significantly altered. There were no toxicologically relevant effects in treated animals with respect to food consumption, clinical chemistry, haematology, absolute and relative organ weights. No treatment-related lesions were detected in histopathology. Particularly, there were no macroscopic or microscopic findings of microemboli or inflammation in any tissue, including the spleen, intestinal wall and GALT. Polarised light examination revealed a lack of birefringent cellulose particles in all organs and tissues from all high-dose rats, indicating no intestinal uptake. According to the authors, the NOAEL of this subchronic gavage study was 5,000 mg/kg bw per day, the highest dose tested. The Panel agreed with this conclusion. The Panel noted that the test substance was not compliant with the specifications of microcrystalline cellulose (E 460(i)) used as food additive.

4.2.2.2. Powdered cellulose (E 460(ii))

Rats

In a subacute feeding study performed according to current standards, fermentation-derived cellulose (60% purity, mixed with 20% sodium carboxy methyl cellulose and 20% sucrose; white powder) was administered to groups of six male and six female F344 rats at dietary levels of 0, 1.25, 2.5 or 5.0% for 28 days (equal to 1,340, 2,644 or 5,331 mg/kg bw per day for males and 1,280, 2,611 and 5,230 mg/kg bw per day for females) (Hagiwara et al., 2010). The treatment had no effects on clinical signs, mortality, body weight, food and water consumption. No adverse effects were detected in urinalysis, ophthalmology, haematology, blood biochemistry and histopathology. Slightly increased absolute and relative caecum weights were measured at necropsy in females ingesting ≥ 2.5% dietary level. This effect was considered by the authors to be a physiological adaptation to the poorly absorbed cellulose. The authors concluded that the NOAEL was 5.0% of the test item in the diet, equal to 5,331 mg/kg bw per day for males and 5,230 mg/kg bw per day for females. The Panel agreed with this conclusion.

The addition of 15% cellulose to the diet of six male rats for 5 weeks did not produce clinical signs of toxicity or statistically significant changes on body weight gain when compared with animals that received a fibre-free diet (Shiau and Ong, 1992). Food intake was significantly increased in cellulose-treated animals, probably due to the high concentration of non-nutritive material in the diet.

In a feeding study with Elcema® (a mixture of four types of α-cellulose in the ratio of 1/1/1/1 (particle size 1–50 μm (powder), 1–100 μm (powder), 1–150 μm (fibrillar), 90–250 μm (granulate)), groups of male and female Wistar rats (n = 20/sex per group) were fed for 90 days at a dietary level of 0% or 10% (equivalent to 0 or 9,000 mg/kg bw per day) (Ferch, 1973a,b, 1974). Statistical analysis of results was not performed. Treated rats gained less weight than those in the control group (> 10% reduction in males and maximal 8% in females). Food consumption was not affected. No treatment-related mortality and behavioural abnormalities were observed. Urinalysis, haematology and clinical chemistry at week 0, 6 and 13 revealed similar results for test and control groups. At necropsy, some of the treated rats had distended stomachs, which often contained considerable amounts of the test diet. The absolute liver and kidney weights of male rats and the ratio of the weight of these organs to brain weight were decreased in test animals (no data about statistical significance). No treatment-related histopathological effects were reported (totally 31 organs examined, no further data). The effects on liver and kidney weight were considered by the authors to be without toxicological relevance, since no effects were detected in histopathology and clinical chemistry. Overall, no toxic effects were induced in this subchronic feeding study in rats at a dose of 10% α-cellulose in the diet (equivalent to 9,000 mg/kg bw per day), the highest dose tested. The Panel agreed with the NOAEL of 9,000 mg/kg bw per day proposed by the authors. The Panel noted that the test substance was not compliant with the specifications of powdered cellulose (E 460(ii)) used as food additive.

Rats (15/sex per group) received 0% or 10% cellulose powder in the diet (equal to 8,200 mg/kg bw per day for male rats and 9,800 mg/kg per day for female rats) for 3 months (Rowland et al., 1982). Rats given the cellulose powder exhibited higher food consumption than control animals, presumably due to the high concentration of non-nutritive material in their diet. No effects were observed on the following parameters: body weight, water intake, haematology, clinical chemistry, urinalysis, organ weights or histopathology.

A group of 20 male and 20 female Crl:CDBR rats received for 13 weeks a basal diet containing a mixture of 10% powdered cellulose (Solka-Floc®, no further data) (equivalent to 9,000 mg/kg bw per day) and 10% fructose; concurrent controls were fed the basal diet (Kruger et al., 1999). All rats were checked once daily for clinical signs. Body weight and food consumption were measured once weekly. Haematological and clinical chemistry parameters were determined in blood collected just prior to necropsy. Macroscopic and microscopic pathology was performed. Histopathology of 34 organs and all gross lesions was performed. No clinical signs were detected and all rats survived to study termination. No effects were reported on body weight. Treated rats apparently consumed more food to compensate for the reduction in caloric intake. The treatment induced no significant haematological or clinical chemistry effects and no changes in organ weights (determined in liver, kidney, adrenals, testes, brain, heart, thymus, spleen, thyroid, epididymal fat pads, mesenteric lymph nodes). No treatment-related effects were reported in the histopathology. No adverse effects were induced in rats receiving a diet supplemented with 10% powdered cellulose (equivalent to 9,000 mg/kg bw per day) for 13 weeks.

The effects of a synthetic diet (AIN-76™) containing 5% cellulose (equivalent to 2,500 mg/kg bw per day; no further details) were compared with a cereal-based diet (4.5% crude fibre, no further details) in female rats (n = 6 per group) (Bieri et al., 1977). After an exposure period of 24 weeks, no effects were noted on terminal body weight, absolute and relative organ weight of liver and kidney or haemoglobin and haematocrit values. No further parameters were measured.

Groups of 10–15 male Sprague–Dawley rats were fed diets containing 0%, 10%, 20% or 30% cellulose fibre (equivalent to 0, 5,000, 10,000 or 15,000 mg/kg bw per day; no further details), for 23 weeks (Nigro et al., 1979). A slight increase in body weight (measured every fourth week) was found at the low dose, but a dose-dependent decrease was observed at ≥ 20% in the diet, significant at the high dose level (30%). Food consumption was increased at ≥ 20% and faecal wet weight increased in all treatment groups. No further parameters measured.

4.2.2.3. Methyl cellulose (MC; E 461)

Rats

Groups of five male and five female rats (not further specified) were dosed via diet with 0 or 10% of MC (4,000 cP) (equivalent to 0 or 9,000 mg/kg bw per day) for 95 days. In females, the feed intake was decreased, resulting in decreased body weight gains (107 vs 125 g in controls). At study termination on day 95, the rats were autopsied and tissues were examined microscopically. The dosing had no adverse effects on relative organ weights of heart, liver, spleen and kidneys. However, the stomachs of the dosed rats were 15% heavier compared with controls. There were no significant microscopic changes indicative of toxic effects in the examined visceral organs (not further specified) (Tainter, 1943).

In two 90-day studies, groups of 10 male and 10 female Sprague–Dawley rats were dosed via diet with 0%, 1%, 3% and 10% low viscosity (10 cP) MC (equivalent to 0, 900, 2,700 or 9,000 mg/kg bw per day) or with 0%, 3% and 10% high viscosity (4,000 cP) MC (equivalent to 0, 2,700 or 9,000 mg/kg bw per day). In both studies, weekly body weight and food consumption records were kept. Haematological evaluations (packed cell volume (PCV), haemoglobin (Hb) determinations and erythrocyte and total and differential leucocyte counts) were conducted during week 12 on five male and five female rats from controls and high-dose rats. Urine analyses were performed in five rats of each sex fed 0% and 10% of the test material. Blood urea nitrogen (BUN), serum alkaline phosphatase (AP) and serum glutamic-pyruvic transaminase were determined terminally. At termination, weights of brain, heart, liver, kidneys and testes were recorded and gross examinations were carried out on all rats. Histopathology was conducted on haematoxylin-eosin-stained sections of selected tissues from rats fed the control and 10% diets. Most, or all, of the following tissues were examined: thyroid, pituitary, trachea, lung, aorta, heart, liver, kidneys, adrenals, spleen, pancreas, stomach, small and large intestine, reproductive organs, urinary bladder, brain, spinal cord, peripheral nerve, skeletal muscle, bone marrow, mesenteric and mediastinal lymph nodes and any lesions suggesting a possible pathological change. Male rats receiving diets containing 10% low viscosity MC (10 cP) showed a significant decrease in their mean starved body weight at autopsy ($p < 0.05$). The average weights, in grams, of few of the organs from these rats were also significantly lower than controls. Especially in male rats dosed with ≥ 3% of low and high viscosity MC, a dose-dependent and significantly increased feed consumption was noted. For all other investigated parameters, no adverse effects were reported (McCollister et al., 1973). In both trials, there were no significant adverse effects at a dose level of 3% (equivalent to 2,700 mg/kw bw per day).

4.2.2.4. Ethyl cellulose (EC; E 462)

Rats

In an unpublished study with rats, no adverse effects were reported in 80 animals dosed via diet with 1.2% of EC (equivalent to 1,080 mg/kg bw per day) (Hake and Rowe, 1963; cited in JECFA, 1990).

4.2.2.5. Hydroxypropyl cellulose (HPC; E 463)

Rats

Groups of 10 young adult male and 10 female Wistar rats were administered daily doses of 0, 1,500, 3,000 or 6,000 mg/kg bw of HPC via gavage for 30 days. The rats were weighed every day and food consumption was measured twice a week during the experiment. After 30 days, blood samples were collected for the following tests: aspartate aminotransferase (serum glutamic-oxaloacetic transaminase (S-GOT)), alanine aminotransferase (serum glutamate-pyruvate transaminase (S-GPT)), total cholesterol, AP, blood sugar, total protein, haematocrit, Hb, white blood cell (WBC) and red blood cell (RBC) counts and specific gravity of whole blood and blood plasma. Furthermore, urine of the individual rats was collected for the qualitative detection of glucose, protein and pH. Then the rats were autopsied and the wet weight of liver, kidneys, heart, spleen, brain (including cerebellum), lungs, adrenals and testes or ovaries were recorded. For histopathological examination, besides these organs, stomach, small intestine and bone were also prepared. For all examined parameters, no adverse effects were reported (Kitagawa et al., 1976b).

In an unpublished study, groups of five male and five female rats were dosed via diet with 0, 0.2, 1 or 5% of HPC (equivalent to 0, 180, 900 or 4,500 mg/kg bw per day) over 90 days. The dosing caused no adverse effects on mortality, growth, food utilisation, urinalysis, haematological indices, organ weight, gross pathology and histopathology. Higher dietary levels (not further specified) resulted in increased food consumption and decreased food utilisation due to the inertness of the material (Industrial Bio-Test Lab, 1963; cited in JECFA, 1969).

4.2.2.6. Hydroxypropyl methyl cellulose (HPMC; E 464)

Rats

Groups of five male Wistar rats were dosed via diet with 0 or 10% of HPMC over 12 days and at termination, caecum and ascending colon were removed (Wyatt et al., 1988). The dosing caused an up to fivefold increase in the wet weights of the full and empty caecum and ascending colon and a decrease in the density of bacteria in the caecum and colon. HPMC was poorly fermented by caecal and colonic bacteria *in vitro,* with only 5% of the substrate being utilised after 7 days of incubation (no significant change in the level of reducing-ends in the culture fluid). The authors concluded that caecal and colonic enlargement was due to tissue hypertrophy in response to increased bulk of contents, and that it is unlikely that SCFA or other microbial metabolites are the stimulus for the trophic response.

In a study with weanling rats (no further data), groups of 10 male and 10 female rats were dosed via diet with 0%, 2%, 10% or 25% of HPMC (equivalent to 0, 2,400, 12,000 or 30,000 mg/kg bw per day) over 30 days (Hodge et al., 1950). The highest dose level caused diarrhoea and a decrease in body weights; three of 10 males and six of 10 females died. At this dose level, there was also a minor decrease in red blood cell counts, while other haematological and also urine parameters, as well as organ weights, were unchanged. A histopathological examination revealed no adverse effects.

In an additional study, groups of 10 male and 10 female young Wistar-derived rats were dosed via diet with 0%, 1%, 3%, 10% or 30% (equivalent to 0, 900, 2,700, 9,000 or 27,000 mg/kg bw per day) of HPMC over 121 days (McCollister and Oyen, 1954). All rats were weighed twice weekly during the study and examinations included general appearance, mortality and average daily food consumption. Whenever possible, failing animals were sacrificed when moribund. Terminal haematological values were obtained from a group of five female control rats and five female rats dosed with 10% HPMC. At termination, all surviving rats were killed and examined. The livers and kidneys from each rat were weighed. Haematoxylin-eosin-stained sections from these organs, as well as from the pancreas, lung, heart, spleen, testes and adrenals were prepared for histologic examination. At a dose level of 30%, body weight gain was markedly decreased and four male and six female rats died during the study due to undernourishment. In male rats dosed with 10%, there also was a slight body weight gain retardation. No other adverse effects were reported and the histological examination revealed no abnormalities in any of the different groups.

In two follow-up studies, groups of 10 male and 10 female young Wistar-derived rats were dosed via diet with 0%, 0.3%, 1%, 3%, 10% or 20% of HPMC containing 24–27% methoxyl groups and 3–5.5% hydroxypropoxyl groups (equivalent to 0, 270, 900, 2,700, 9,000 or 27,000 mg/kg bw per day) for 90 days or with HPMC containing 19–24% methoxyl groups and 4–12% hydroxypropoxyl groups for 84 days (McCollister et al., 1961). During the studies, the rats were observed frequently for changes in gross appearance and behaviour. Body weights were determined twice weekly and average food consumption per rat was recorded. At termination, gross pathological examinations were performed, and the lungs, heart, liver, kidneys, testes and spleen were removed and weighed. Portions of these tissues, as well as adrenals and pancreas, were prepared for a microscopic examination. In addition, blood haematocrit values were determined. In the first study, three rats of each sex died after dosing with 20% and there was a marked reduction in body weight gain in both sexes. In male rats, a significant retardation in body weight gain was seen at 10%. In none of the dosed animals, were adverse histopathologic effects noted. Also, in the second study, male rats showed a significant retardation of body weight gain at the 20% level and a slight retardation at 10%. As a result of undernourishment, there were also corresponding changes in liver, kidney and testes weights. The gross and microscopic examination gave no indications for adverse effects and there were no changes in haematocrit values. In both trials, there were no significant adverse effects at a dose level of 3% (equivalent to 2,700 mg/kg bw per day).

In an additional, unpublished study, groups of 10 male and 10 female young rats (unknown strain) were dosed via diet with 0%, 1%, 3% and 10% of HPMC (higher viscosity; 31,800 cP) and with 0%, 1%, 3% and 10% of HPMC (lower viscosity; 8,480 cP) (equivalent to 0, 900, 2,700 or 9,000 mg/kg bw per day) over 92 days (McCollister and Copeland, 1967; cited in JECFA, 1990). The treatment gave no adverse effects concerning mortality, growth, general appearance and behaviour, body weights, food consumption, haematological and clinical chemistry analysis, organ weights and at gross and histological examination.

In two other 90-day studies, groups of 10 male and 10 female Dow-Wistar rats were dosed via diet with 0%, 1%, 3% and 10% low viscosity (10 cP) HPMC or with 0%, 3% and 10% high viscosity (4,000 cP) HPMC (equivalent to 0, 900, 2,700 or 9,000 mg/kg bw per day) (McCollister et al., 1973). No adverse effects concerning mortality, body weight gain, food consumption, urine and haematological analyses and serum chemistry were noted. Terminal absolute and relative organ weights showed no treatment-related effects. The gross and histopathological examination of the tissues revealed similar findings for control and treated rats. At all dose levels (i.e. up to 9,000 mg/kg bw per day), no adverse effects were reported in both studies.

Groups of 15 male and 15 female young Sprague–Dawley rats were dosed via diet with 0%, 1% or 5% low viscosity (4.22 cP) HPMC (equivalent to 0, 900 or 4,500 mg/kg bw per day) for 90–91 days (Schwetz, 1976). No adverse effects concerning mortality, body weight gain, food consumption, urine and haematological analyses and serum chemistry were noted. Terminal absolute and relative organ weights showed no treatment-related effect. The gross and histopathological examination of the tissues revealed similar findings for control and treated rats. For none of the examined parameters were adverse effects reported at a dose level up to 4,500 mg/kg bw per day.

Groups of five male and five female Crj:CD (SD) IGS rats (SPF) with an age of about 5 weeks and body weights of 125–176 g were dosed via gavage with 0, 505, 1,020 or 2,100 mg/kg bw per day of HPMC (viscosity of 2.83 mPa.s) for 91 days (Obara et al., 1999). For both high-dose male and female rats, lower body weights were observed from day 28 onwards; in high-dose males there was also a decrease in food consumption and urine volume. However, these differences were not statistically significant. For all other examined endpoints, no treatment-related effects were noted. Based on the decrease in body weights, the authors of this study identified a NOAEL value of 1,020 mg/kg bw. However, the Panel considered the level of 2,100 mg/kg bw per day as the NOAEL, because the effects observed were all not statistically significant.

Rabbits

In groups of six rabbits (approximately 6 months old and with a body weight of 1.8 kg) dosed via diet with 0%, 10% or 25% of HPMC (equivalent to 0, 3,000 or 7,500 mg/kg bw per day) over 30 days, no adverse effects concerning body weights, urine analysis, haematology, organ weights and histological examination were reported (Hodge et al., 1950).

Dogs

Two dogs (body weights of 11 and 13 kg) were dosed with 25 or 50 g/day, respectively, of HPMC over 30 days (Hodge et al., 1950). In the higher dose animal, effects such as diarrhoea, slight weight loss and slight depression in RBC count were noted, while the lower dose in the other animal was well tolerated. An urine analysis and a histological examination revealed no adverse effects at both dose levels.

In another study, groups of two male and two female beagle dogs were dosed via diet with 0, 2 and 6% low viscosity (10 cP) HPMC for 90 days (equivalent to 0, 500 or 1,500 mg bw per day) (McCollister et al., 1973). Body weights and food consumption were recorded weekly. Before starting the study and at termination on day 90, standard haematological and clinical chemistry parameters (PCV, Hb, RBC, total and differential WBC, BUN, AP, S-GOT, S-GPT and bromosulfothalein retention) were determined and also tissues from all dogs were examined. No adverse effects concerning mortality, body weight gain, food consumption, urine and haematological analyses and serum chemistry were noted. Terminal absolute and relative organ weights showed no treatment-related effect. The gross and histopathological examination of the tissues revealed similar findings for control and treated dogs. There was no evidence of storage of the test material within the cells of the reticuloendothelial system of the dosed animals.

Groups of four male and four female adult beagle dogs were dosed via diet with 0, 1 or 5% low viscosity (4.22 cP) HPMC (equivalent to 0, 250 or 1,250 mg/kg bw per day) for 90–91 days (Schwetz, 1976). No adverse effects concerning mortality, body weight gain, food consumption, urine and haematological analyses and serum chemistry were noted. Terminal absolute and relative organ weights showed no treatment-related effects. The gross and histopathological examination of the tissues revealed similar findings in control and treated dogs. For none of the examined parameters, were adverse effects reported.

4.2.2.7. Ethyl methyl cellulose (EMC; E 465)

No data available.

4.2.2.8. Sodium carboxy methyl cellulose (NaCMC; E 466)

Rats

Groups of five male Wistar rats were dosed via diet with 0% or 10% of CMC (equivalent to 0 or 12,000 mg/kg bw per day) over 12 days, and at termination caecum and ascending colon were removed (Wyatt et al., 1988). Dosed rats showed diarrhoea from the second day of dosing and a significantly increased output of faecal material. There was a visible enlargement of the caecum and increased wet weights of contents and tissues (almost eightfold increase in weight of caecal contents coupled with a doubling of tissue weight). The dosing had no significant effect on the density of bacteria in the caecum and colon. The aerobic microflora of the control group was composed primarily of *Streptococcus* spp. (95–100% of isolates), while both in caecal and colonic contents of CMC-dosed rats, almost exclusively *E. coli* was found (93% of isolates). No enterotoxin activity was detected in the *E. coli* strains isolated from CMC-fed rats with diarrhoea, and serotyping showed that the strains (O54 and O24) belonged to groups that are not commonly associated with diarrhoea in man. A substantial amount of unfermented CMC was present in the intestinal contents of dosed rats and the proportion of CMC increased distally. CMC appeared not to have been hydrolysed to shorter chain lengths, as no increase in reducing ends could be demonstrated compared with animals maintained on the control diet. CMC also was poorly fermented by caecal and colonic bacteria *in vitro*. By day 7 of incubation, there was only a very slight increase in the level of reducing-ends in the culture fluid and dosed rats had significantly lower SCFA concentrations in the caecum. The authors concluded that caecal and colonic enlargement was due to tissue hypertrophy in response to increased bulk of contents and that it was unlikely that SCFA or other microbial metabolites were the stimulus for the trophic response.

In an unpublished study, 12 rats/per group (not further specified) were dosed over 21 days with a high-protein diet containing 0% or 15% sodium CMC of 10 viscosity grades (35–4,500 cP) or four other vegetable gums (Anderson, 1986; cited in JECFA, 1990). Animals were weighed on alternate days. Body weight gain in animals dosed with one sample of CMC exceeded that of controls and body weight gains in animals dosed with two other CMC samples were less than that of controls. Average faecal water content (measured as %) was increased in all CMC-fed animals from 1.9- to 3-fold, and average filled caecal weight (g/kg bw) was increased 1.5- to 3.3-fold, compared to controls. It was noted that there was a tendency for CMC samples of low molecular weight to produce high faecal wet

weights. Measurement of the viscosities of completely hydrated samples of CMC indicated that CMC can have large or narrow molecular weight distributions. It was suggested that different molecular weight distributions in samples of CMC may produce different physiologic or dietary responses.

In a study with young male Sprague–Dawley rats (3-weeks old) with conventional gut microflora, six animals per group were dosed via diet with 0% or 5% of CMC (equivalent to 0 or 6,000 mg/kg bw per day) over 4 weeks (Mallett et al., 1984). At termination, the caecal contents from each animal were collected and used for different enzyme assays. In dosed rats, the body weights were decreased (about 9%) compared to the control group, and the weights of both the caecal wall and caecal contents were significantly increased. The treatment significantly increased the total bacterial population of the caecum and the mean caecal ammonia concentration was increased fourfold. All measured enzyme activities (azoreductase, β-glucosidase, β-glucuronidase, nitrate reductase, nitro reductase and urease) were also significantly increased compared to controls. The authors assumed that the β-1,4-glucose backbone of CMC was susceptible to attack by gut bacteria.

In groups of three young rats (no further data), the dosing with 0% or 14% of CMC (equivalent to 0 or 16,800 mg/kg bw per day) via diet over 5 weeks caused no adverse effects (Ziegelmayer et al., 1951).

In a study with limited documentation, the daily dosing of 10 rats (no further data) with 300–500 mg of CMC over 2 months caused no adverse effects (Werle, 1941).

In another study, 10 female Wistar rats with an age of 82–98 days were fed a diet containing 20% CMC (equivalent to 18,000 mg/kg bw per day) for 63 days (Rowe et al., 1943). All animals were weighed twice weekly and individual weight records were kept throughout the experimental period. The treatment caused slight growth retardation and a laxative effect was observed. Organ weights and gross examination revealed no abnormalities. Also, the results of a histopathological examination of the liver, kidney, spleen, pancreas and adrenal gland revealed no significant differences between the treated and the control groups.

Groups of albino Wistar outbred rats [Crl:WI(WU)BR] (20/sex, 8 weeks of age) were dosed via diet with 0, 2.5, 5 and 10% of CMC (equivalent to 0, 2,250, 4,500 or 9,000 mg/kg bw per day) for 91–95 days in male rats and for 98–102 days in female rats (Bär et al., 1995a). To adapt the animals of the mid- and high-dose groups, the dose of CMC was increased gradually from 2.5% on days 1–3 to 5% on days 4–7 and to 10% from day 7 onwards. The mean intakes were 0, 1,360–1,570, 2,810–3,230 or 6,150–6,800 mg/kg bw per day (higher values are for female rats) and the dietary sodium content was 0.31%, 0.57%, 0.81% and 1.27%. In general, the ingestion of CMC was well tolerated, except that all high-dosed rats had some diarrhoea during the entire study period. In both sexes, there was a dose-dependent increase in food intake, although in high-dosed females the body weights were slightly below control values. Also, the water intake was dose dependently increased in both sexes and was statistically significant in low-dosed males and in mid- and high-dosed rats of both sexes. In high-dosed female rats, the activity of plasma AP was significantly increased, while in high-dosed male rats, the alanine aminotransferase activity was significantly increased. As a result of the higher water intake, urine volumes in both sexes also increased dose dependently. In addition, a dose-dependent increase of sodium, calcium and citrate in urine was seen at ≥ 5% CMC (equivalent to 4,500 mg/kg bw per day). Terminal body weights did not differ significantly between treated groups and controls. The dosing caused some changes in absolute or relative organ weights of liver and kidneys, but especially for the caecum weights, there was a clear dose-dependent increase both in male and female rats. A gross examination at autopsy revealed the presence of caecal enlargement and an increased liquid content in the intestinal tract, particularly in high-dosed male and female rats. On microscopic examination, an increased incidence of dilatation of the colon was observed in high-dosed females. The renal observations included an increased occurrence of pelvic urothelial hyperplasia (5 out of 20 rats) and pelvic nephrocalcinosis (6 out of 20 rats) in low-dosed male animals. Corticomedullary nephrocalcinosis was seen in five of out 20 high-dosed female rats. In the bladder of male rats, an increased incidence of diffuse epithelial hyperplasia was found in 8 out of 20 high-dosed rats. For all the reported findings, a toxicological concern was not concluded, as the findings in the GI tract were considered to be a consequence of the accumulation of poorly absorbed water-soluble material in the caecum and colon, while the findings in kidneys and urinary bladder were attributed to the four times higher concentration of sodium in the CMC diet compared with the basal diet.

Dogs

In a study with dogs, aged about 16 weeks (not further specified), three groups of 10 animals each were dosed with 0, 500 or 1,000 mg/kg bw per day of CMC via diet for 6 months (Shelanski and Clark, 1948). None of the animals died during the course of the study. The dosing was well tolerated and

caused no changes in body weights. At study termination, all dogs were autopsied; the histological examination of stomach, intestines, spleen, liver, kidney, heart, lung and pancreas revealed no changes.

4.2.2.9. Cross-linked sodium carboxy methyl cellulose (E 468)

Rats

Cross-linked sodium carboxy methyl cellulose was administered to Sprague–Dawley CD rats (20 animals/sex, 8 weeks old) at 0, 10,000 or 50,000 mg/kg diet for 90 days (equal to 757 and 893 or 3,922 and 4,721 mg/kg bw per day for males and females, respectively) (Freeman et al., 2003). The study was conducted according to a current OECD guideline and in compliance with Good Laboratory Practice (GLP). A control group of 20 animals were given a basal diet. No treatment-related deaths took place and no clinical signs were reported in response to the test article administration. The body weights were significantly reduced in males receiving 50,000 mg/kg during the last 3 weeks of the study (p value not stated). The food consumption of females receiving the 50,000 mg/kg dose was significantly increased (p value not stated) compared to controls during most of the study (data not shown). No effects were seen in the clinical chemistry or haematology investigations, no treatment-related findings were noted in the necropsy and there were no effects on organ weights or organ-to-brain ratios. The study authors concluded that the daily administration of 50,000 mg/kg cross-linked sodium carboxy methyl cellulose did not result in adverse effects in rats following 90-day exposure, and the NOAEL was concluded to be 3,922 mg/kg bw per day for males and 4,721 mg/kg bw per day for females.

Dogs

In a 1-year study, groups of two dogs (strain and sex not further specified) were dosed with 0, 100, 300, 1,000 or 3,000 mg cross-linked sodium carboxy methyl cellulose/kg bw per day. The treatment had no adverse effects on body weights and none of the animals died. Urine analyses (performed twice monthly) and haematological examinations performed prior to starting, four times during the experiment and terminally, showed no changes. At necropsy, organ weights were recorded and a number of tissue sections (heart, lung, spleen, stomach, large and small intestine, pancreas, liver, gall bladder, adrenal, kidney, bladder, gonads, thyroid, bone marrow and brain) were examined microscopically. No adverse effects were reported (Hodge et al., 1950).

4.2.2.10. Enzymatically hydrolysed carboxy methyl cellulose (E 469)

Rats

Groups of albino Wistar outbred rats [Crl:WI(WU)BR] (20 per sex, 8 weeks of age) were dosed via diet with 0%, 2.5%, 5% and 10% of enzymatically hydrolysed carboxy methyl cellulose for 91–95 days for male rats and for 98–102 days for female rats (Bär et al., 1995a). To adapt the animals of the mid- and high-dose groups, the dose of enzymatically hydrolysed carboxy methyl cellulose was increased gradually from 2.5% on days 1–3, to 5% on days 4–7, and to 10% from day 7 onwards. The mean intakes were equal to 0, 1,340–1,560, 2,830–3,170 or 5,920–6,610 mg/kg bw per day (higher values are for female rats) and the dietary sodium content was 0.31%, 0.51%, 0.72% and 1.16%. In general, the ingestion of enzymatically hydrolysed carboxy methyl cellulose was well tolerated, except that all high-dosed rats had some diarrhoea during the entire study period. In both sexes, there was a dose-dependent increase in food intake, although in high-dosed females the body weights were slightly below control values. Also, the water intake was dose-dependently increased and the differences were statistically significant in mid- and high-dosed rats of both sexes. In high-dosed females, Hb concentrations and PCVs were slightly decreased (details were not provided). Plasma AP activity was significantly increased in high-dosed male rats and in mid-dosed female rats. As a result of the higher water intake, urine volumes also increased with increasing doses of enzymatically hydrolysed carboxy methyl cellulose in male and female rats. In addition, a dose-dependent increase in sodium, calcium and citrate was seen at $\geq$ 2.5% enzymatically hydrolysed carboxy methyl cellulose. Terminal body weights did not differ significantly between treated groups and controls. The dosing caused some slight changes in absolute or relative organ weights of liver and kidneys, but especially for the caecum weights, there was a clear dose-dependent increase both for male and female rats. Gross examination at autopsy revealed the presence of caecal enlargement and an increased liquid content in the intestinal tract, particularly in high-dosed male and female rats. On microscopic examination, an increased incidence of dilatation of the colon was observed in high-dosed females. The renal observations included an increased occurrence of pelvic urothelial hyperplasia in males

dosed with 10% (6 out of 20 rats) and pelvic nephrocalcinosis at ≥ 5% in males (five or nine of 20 rats). In the bladder of male rats, an increased incidence of diffuse epithelial hyperplasia was found in five of 20 high-dosed rats. For all the reported findings, a toxicological concern was not concluded, as the findings in the GI tract were considered to be a consequence of the accumulation of poorly absorbed water-soluble material in the caecum and colon, and the findings in kidneys and urinary bladder were attributed to the four times higher concentration of sodium in the enzymatically hydrolysed carboxy methyl cellulose diet compared with the basal diet.

4.2.2.11. Summary

Data are available for microcrystalline cellulose, powdered cellulose, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, sodium carboxy methyl cellulose and enzymatically hydrolysed carboxy methyl cellulose.

- The subacute and subchronic toxicity of microcrystalline and powdered cellulose was low. The NOAELs found in oral studies (gavage, drinking water or diet) in rats ranged from 3,769 to 9,000 mg microcrystalline cellulose/kg bw per day (5–10% in the diet) and 9,000 mg powdered cellulose/kg bw per day (the highest dose tested in each case). No effects were detected when an increased percentage of particles below the recommended particle size in the EU specifications was present in the test substance.
- In two 90-day feeding studies, groups of 10 male and 10 female Sprague–Dawley rats were dosed via diet with 0%, 1%, 3% and 10% low viscosity (10 cP) methyl cellulose or with 0%, 3% and 10% high viscosity (4,000 cP) methyl cellulose. In high-dosed male rats, a significant decrease in body weights was noted, while for all other investigated parameters no adverse effects were reported (McCollister et al., 1973). Therefore, a NOAEL value of 3% (equivalent to 2,700 mg/kw bw per day) was derived from this study.
- In a 30-day gavage study, groups of 10 young adult male and female Wistar rats were dosed with 0, 1,500, 3,000 or 6,000 mg/kg bw of hydroxypropyl cellulose. Even at the highest dose level, no adverse effects were reported (Kitagawa et al., 1976b).
- In two 90-day feeding studies, groups of 10 male and 10 female Dow–Wistar or Sprague–Dawley rats were dosed via diet with 0%, 1%, 3% and 10% low viscosity (10 cP) hydroxypropyl methyl cellulose or with 0%, 3% and 10% high viscosity (4,000 cP) hydroxypropyl methyl cellulose. In both trials, even at the highest dose level of 10% (equivalent to 9,000 mg/kg bw per day), no adverse effects were reported (McCollister et al., 1973).
- In another study, groups of five male and five female Crj:CD (SD) IGS rats (SPF) were dosed via gavage with 0, 505, 1,020 or 2,100 mg/kg bw per day of hydroxypropyl methyl cellulose (viscosity of 2.83 mPa.s) for 91 days. Apart from a decrease in body weights in high-dosed male and female rats, which was not statistically significant, no treatment-related effects were noted for all the other endpoints examined. The food consumption data were limited, but suggested decreased food consumption. The authors of this study gave a NOAEL value of 1,020 mg/kg bw (Obara et al., 1999). The Panel considered 2,100 mg/kg bw per day of hydroxypropyl methyl cellulose as the NOAEL in this study.
- In two parallel studies, groups of 20 Albino Wistar outbred rats [Crl:WI(WU)BR] per sex were dosed with carboxy methyl cellulose or enzymatically hydrolysed carboxy methyl cellulose via diet with 0%, 2.5%, 5% and 10% (equal to 0, 1,500, 3,000 and 6,000 mg/kg bw per day) for up to 102 days (Til, 1992; Bär et al., 1995a). Although, in both studies, some effects (increased caecum weights, urothelial hyperplasia, pelvic nephrocalcinosis, corticomedullary nephrocalcinosis, increased incidence of diffuse epithelial hyperplasia in the urinary bladder) were observed, for all the reported findings, a toxicological concern was not concluded for carboxy methyl cellulose or enzymatically hydrolysed carboxy methyl cellulose itself, as the findings in the GI tract were considered to be a consequence of the accumulation of poorly absorbed water-soluble material in the caecum and colon, and the findings in kidneys and urinary bladder were attributed to the up to fourfold higher concentration of sodium in the fed diet compared with the basal diet.

Several additional studies, which do not meet current criteria for toxicological testing or which were not available (unpublished data) for evaluation, supported the low toxicity of this group of modified celluloses.

Although there were some inconsistencies in the data, the main effects seen were decreases in body weight gain at the highest dose, which are likely to be due to the amount/bulk of cellulose in the

diet decreasing the nutrient intake. The NOAEL values reported ranged from 2,000 up to 9,000 mg/kg bw per day.

4.2.3. Genotoxicity

4.2.3.1. Microcrystalline cellulose (E 460(i))

In vitro

Avicel® RCN-15 (a mixture of 85% microcrystalline cellulose with 15% guar gum, no further data) was not mutagenic in a bacterial reverse mutation assay in the *Salmonella* Typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 when tested as suspension in dimethylsulfoxide (DMSO) at five dose levels between 50 and 5,000 μg/plate, with and without metabolic activation by rat liver S9-mix in an unpublished study performed in compliance with GLP (Batt, 1992).

The same test system resulted also in no mutagenic activity with the test substance Avicel® AC-815 (composed of 85% microcrystalline cellulose and 15% calcium alginate). In this study, *E. coli* WP2uvrA or *S.* Typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to the test substance suspended in DMSO at doses from 10 to 5,000 μg/plate in the presence or absence of metabolic activation with rat liver S9-mix (Documentation provided to EFSA n. 37).

In a third bacterial reverse mutation assay, using *S.* Typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538, microcrystalline cellulose suspended in DMSO produced no increase in revertants at doses up to 5,000 μg/plate (no further information available) (FMC, 1991; referred to by SCF, 1999).

Avicel® RCN-15 was tested in a mammalian gene mutation assay in L5178Y mouse lymphoma cells in an unpublished study performed in compliance with GLP (Cifone, 1992). The test material was dissolved in DMSO at 100 mg/mL and tested in replicated experiments at six dose levels, ranging from 100 to 1,000 μg/mL (top concentration based on the 1% final concentration of DMSO in culture medium) both with and without metabolic activation. In both cases, a 4-h treatment was applied. No toxicity and no increase in forward mutation at the thymidine kinase locus which was dose-related or exceeded twice the solvent control was observed. Precipitation in culture medium was observed above 100 μg/mL. Positive control substances, methyl methansulfonate and 3-methylcholanthrene, elicited a distinct mutagenic response. The Panel noted that an extended treatment without metabolic activation was not performed, but this was not recommended in the relevant OECD Guideline at the time the study was performed. In another study, also Avicel® CL-611 was tested with negative results in the same test system (Documentation provided to EFSA no. 34).

Avicel® RCN-15 was tested in an unscheduled DNA synthesis assay in rat liver primary cells in an unpublished study performed in compliance with GLP (McKeon, 1992). The test substance was formulated in DMSO and applied at seven concentrations in the range 5–1,000 μg/mL in a first trial and at 10 concentrations in the range 10–1,000 μg/mL in a second trial. Precipitation was observed from 5 μg/mL onwards in the first trial and from 10 g/mL onwards in the second trail. No overt toxicity (i.e. < 78 of survival) and no induction of unscheduled DNA synthesis was observed in both experiments. The positive control 2-acetylaminofluorene elicited the expected positive response. The Panel noted that in this study a lower solubility of Avicel® RCN-15 was reported, compared to the previous study by Cifone (1992).

In vivo

Avicel® RCN-15 was tested in a mouse bone marrow micronucleus assay in ICR mice (Murli, 1992). The test material was mixed in a commercial diet at a concentration corresponding to an exposure level of 5,000 mg/kg bw. The feed (1 g) was administered during an exposure time of 10 h, and animals (groups of five males and five females) sacrificed 24, 48, and 72 h after the end of the exposure period. No increase of micronucleated polychromatic erythrocytes and no evidence of toxicity to bone marrow was observed in treated animals. A significant positive response was induced by the positive control cyclophosphamide, administered by gavage 24 h before sacrifice. This study was performed in compliance with GLP.

Negative results were also reported with other microcrystalline cellulose preparations in other unpublished studies (Documentation provided to EFSA n. 35–36).

4.2.3.2. Methyl cellulose (MC; E 461)

In a screening of cosmetic ingredients, MC was tested for mutagenicity in a spot test with *S.* Typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538, with and without metabolic

activation. Negative results were reported by the study authors at the single dose level tested (50 μg/plate) (Blevins and Taylor, 1982).

In another published study, MC was not mutagenic in bacterial reverse mutation assays in *S.* Typhimurium strains TA92, TA1535, TA100, TA1537, TA94 and TA98, with and without metabolic activation, up to the maximum dose of 70 mg/plate (Ishidate et al., 1984). In the same study, MC was not clastogenic in an *in vitro* chromosomal aberration assay in Chinese hamster fibroblasts (CHL), only carried out without metabolic activation, up to the maximum tested concentration of 4 mg/mL. The Panel noted that only a qualitative indication of the outcome of tests, with no presentation of experimental results, was available from the above studies.

Further results of genotoxicity tests on MC are reported in an unpublished study (Litton Bionetics Inc., 1974) on the test material Methocel (FDA 71-264). Negative results were obtained in the following assays:

- two host-mediated assays in rats, dosed once or five times either with 4.75, 47.5 or 475 mg/kg bw by gavage or with 5,000 mg/kg via feed, using *S.* Typhimurium strains TA1530 and G46 and yeast strain D3 as indicator organisms for reverse mutation and mitotic recombination induction, respectively;
- a chromosome aberration assay with human embryonic lung cells (WI-38), only performed without metabolic activation, at doses of 80, 800 and 8,000 μg/mL;
- an *in vivo* chromosome aberration assay in rat bone marrow, following single or repeated (five times) oral administration of the test article, either at 4.75, 47.5 or 475 mg/kg bw by gavage, or at 5,000 mg/kg bw per day via feed;
- a dominant lethal assay with male rats at identical dosage regimen as above.

The Panel noted that these studies, although acceptable at the time they were performed, are based on limited and/or obsolete experimental protocol/system.

4.2.3.3. Ethyl cellulose (EC; E 462)

No data available.

4.2.3.4. Hydroxypropyl cellulose (HPC; E 463)

No data available.

4.2.3.5. Hydroxypropyl methyl cellulose (HPMC; E 464)

No data available.

4.2.3.6. Ethyl methyl cellulose (EMC; E 465)

No data available.

4.2.3.7. Sodium carboxy methyl cellulose (CMC; E 466)

Sodium CMC was not mutagenic in bacterial reverse mutation assays in the *S.* Typhimurium strains TA92, TA1535, TA100, TA1537, TA94 and TA98, with and without metabolic activation up to the maximum dose of 2.5 mg/plate (Ishidate et al., 1984). In the same study, sodium CMC was not clastogenic in an *in vitro* chromosomal aberration assay in CHL, only carried out without metabolic activation, up to the maximum tested concentration of 1 mg/mL. The Panel noted that no raw data were presented for these tests, which were carried out in the framework of a large screening of food additives.

Further results on sodium CMC were available from an unpublished study (Litton Bionetics Inc., 1975, 1980). In this study, sodium CMC was not mutagenic in the following tests:

- bacterial reverse mutation tests with *S.* Typhimurium TA1535, TA1537 and TA1538, both in the presence and the absence of metabolic activation, at concentrations of 2.5–10% (suspension test) and 5 mg/plate (spot test);
- a mitotic recombination assay with *Saccharomyces cerevisiae* D4 at concentrations of 0.25%, 0.5% and 1%, only performed without metabolic activation;

The Panel noted that these studies, although acceptable at the time they were performed, are based on limited and/or obsolete experimental protocol/system.

Negative results in an Ames test with *S.* Typhimurium TA98, TA100, TA1535, TA1537 and TA1538, both in the presence and absence of metabolic activation at doses from 0.5 to 5,000 μg/plate, were

also reported in another unpublished study (Litton Bionetics Inc., 1980), not available to the Panel for evaluation.

4.2.3.8. Cross-linked sodium carboxy methyl cellulose (E 468)

The literature search and the EFSA call for data did not produce any genotoxicity data for cross-linked sodium carboxy methyl cellulose (E 468). The previous evaluation by the SCF (1996) refers to available genotoxicity data, but no further information is available. The most recent evaluation by JECFA (2003) does not discuss the genotoxicity of cross-linked sodium carboxy methyl cellulose (E 468).

4.2.3.9. Enzymatically hydrolysed carboxy methyl cellulose (E 469)

No data available.

4.2.3.10. Summary

Avicel® RCN-15 (a mixture of 85% microcrystalline cellulose with 15% guar gum) did not induce mutagenic effects in the presence or absence of a metabolic activation system in bacterial reverse mutation assays (Batt, 1992), in the mammalian cell gene mutation assays (Cifone, 1992) and in an *in vitro* test for unscheduled DNA synthesis (McKeon, 1992). Avicel® RCN-15 was also tested negative in mouse bone marrow micronucleus assays (Murli, 1992). Negative results were also reported in the following unpublished studies: bacterial reversion assay with Avicel® AC-815 (85% microcrystalline cellulose and 15% calcium alginate) (Documentation provided to EFSA no. 34), *in vivo* micronucleus assays with Avicel® PH-101 (pharmaceutical microcrystalline cellulose, nominal mean particle size of 50 μm) (Documentation provided to EFSA no. 36) and Avicel® CL-611 (Documentation provided to EFSA no. 35). The Panel noted that, even though the majority of these studies were carried out with mixtures containing microcrystalline cellulose and guar gum rather than with microcrystalline cellulose alone, the latter was present as main component (85% by weight) in such mixtures. Therefore, the results of the studies can be considered directly relevant for the evaluation of the genotoxicity of E 460 (i). Based on the negative results reported, the Panel concluded that microcrystalline cellulose (E 460 (i) is not genotoxic. The Panel also considered that this conclusion can be extended to powdered cellulose (E 460(ii)), which is structurally similar to E 460(i) but with a higher polymerisation degree.

Concerning modified celluloses, experimental data on genotoxicity were only available for methyl cellulose (E 461) and sodium carboxy methyl cellulose (E 466).

Both substances were negative in Ames tests with different *S.* Typhimurium strains, both with and without metabolic activation (Litton Bionetics Inc., 1975, 1980, Blevins and Taylor, 1982; Ishidate et al., 1984). Negative results were also obtained in a chromosomal aberration assay in CHL (Ishidate et al., 1984), only performed without metabolic activation, and in host-mediated assays with yeast and bacteria (Litton Bionetics Inc., 1974, 1975).

MC was also tested with negative results in an *in vitro* chromosomal aberration assay in human embryonic lung cells (WI-38), and *in vivo* in a chromosome aberration assay in rat bone marrow and in the dominant lethal assay in male rats (Litton Bionetics Inc., 1974).

The Panel noted that most genotoxicity test results on MC and sodium CMC were from limited and/or briefly reported studies, not available for direct evaluation to the Panel. However, the Panel also noted that there is a long history of use of MC and CMC as vehicles for non-water-soluble substances in *in vitro* and *in vivo* genotoxicity assays (as recommended in OECD TG 478, 2015 and TG 483, 2015). Therefore, the Panel concluded that MC and CMC do not raise concern for genotoxicity.

The Panel also considered that read-across from MC (E 461) to the other modified celluloses bearing similar simple substituents (E 462, E 463, E 464, E 465) was justified, as the SAR analysis of E 462, E 463, E 464, E 465 using the OECD QSAR Toolbox did not highlight any structural alert for genotoxicity in their structure. Thus, the Panel concluded that E 462, E 463, E 464, E 465 did not raise genotoxic concern either.

Similarly, the Panel considered scientifically justified the read-across from sodium CMC (E 466) to its products of enzymatic hydrolysis (E 469) or cross-linking (E 468), which in a similar *in silico* analysis were shown not to bear additional structural determinants of genotoxicity.

Overall, the Panel concluded that microcrystalline cellulose (E 460(i)), powdered cellulose (E 460(ii)) and modified celluloses (E 461–466 and E 468–469) do not raise concern for genotoxicity.

4.2.4. Chronic toxicity and carcinogenicity

4.2.4.1. Microcrystalline cellulose (E 460(i))

Rats

Groups of male and female rats (no further details) received the control diet or a diet containing 330 mg/kg microcrystalline cellulose (equivalent to 16.5 mg/kg bw per day), for a period of 6 months (Yartsev et al., 1989; cited in JECFA, 1990). Six rats per group were then sacrificed, necropsy performed, and tissues processed for histopathology (no further data available). No effects of the treatment were reported.

An unpublished chronic feeding study is reported in the secondary literature (limited information; no further details available). Three groups of 50 male and 50 female rats received in their diet either 30% *'ordinary cellulose'* or microcrystalline cellulose or microcrystalline cellulose gel for 72 weeks (equivalent to 15,000 mg/kg bw per day). The type of control was not specified. No clinical signs were reported. The body weights of males treated with microcrystalline cellulose gel were higher than those of the controls. No such effects were detected with the other cellulose formulations. Food efficiency, survival and haematology were comparable in all groups. The liver and kidney weights of males receiving microcrystalline cellulose gel were increased. Histopathology showed some dystrophic calcification of renal tubules in females on microcrystalline cellulose. All other organs appeared unremarkable. The tumour incidences did not differ between treated and control groups (Documentation provided to EFSA no. 40).

A combined one-generation reproductive/chronic toxicity study was performed in rats (Lewerenz et al., 1979; referred to by SCF, 1999) (Lewerenz et al., 1981a; referred to by SCF, 1999), in which males and females of the F1 generation were fed microcrystalline cellulose (90% of particles < 20 μm) at 0 (control), 30, 100 or 200 g/kg diet (equivalent to 0, 1,500, 5,000 or 10,000 mg/kg bw per day), for up to 2 years (data from secondary sources, no further details available). The treatment induced some growth depression of the F1 rats at the top dose during the early growth phase only. Food consumption was increased in all treated groups. After 12 months, particles were detected in some organs but no microemboli were identified. Some impairment of the renal function without any associated histopathological changes and of some haematological changes in the highest dose group could not be confirmed in the surviving rats treated for 2 years. This study was also reported in the JECFA evaluation (Lewerenz et al., 1981b; referred to by JECFA, 1999a,b). The Committee stated that the available data are not sufficient for evaluation due to the high mortality during the course of the study, the evidence of confounding infection, the limited number of animals for histopathology and the absence of details of the first year of treatment. Limited information on this study was published in a review (Steege et al., 1980) and did not permit a firm conclusion. The Panel agreed with this conclusion.

Initiation–promotion studies

The Panel noted a series of studies which had investigated potential beneficial effects of microcrystalline cellulose administration on the development of cancer in laboratory animals treated with an initiating agent (Freeman et al., 1978, 1980; Nigro et al., 1979; Yamamoto, 1994; Cohen et al., 1996; Chang et al., 1997; Wijnands et al., 1999; Iwane et al., 2002) and a clinical study in humans diagnosed with colon cancer (Hardman et al., 1997). The Panel did not consider these studies relevant to the risk assessment of microcrystalline cellulose as a food additive (E 460(i)).

4.2.4.2. Powdered cellulose (E 460(ii))

Monkeys

Intestinal structure of male adult African Green monkeys (n = 4 per group) was studied after feeding diets containing 10% psyllium husk (fibre; highly branched arabino-xylan-polysaccharide) or 10% cellulose (Cellufil®; no further data) (equivalent to 7,500 mg/kg bw per day), for 3.5 years (Paulini et al., 1987). The cellulose-treated animals did not show any abnormality in the GI tract.

4.2.4.3. Methyl cellulose (MC; E 461)

In a feeding study, groups of five female rats (strain not specified) were dosed via diet with 1.66 or 5% of MC (equivalent to 833 or 2,500 mg/kg bw per day) for 6 months (Bauer, 1945). Adverse effects caused by the treatment were not reported.

In another feeding study, 80 young male and female albino rats were dosed with 0.8% MC in the diet (equivalent to 400 mg/kg bw per day) and with 1% MC via drinking water (equivalent to 900 mg/kg bw per day) for about 9 months (Deichmann and Witherup, 1943). As controls, also 80 young male and female albino rats were used. The combined average total daily intake was calculated to be 436 mg of MC per animal. The dosing was well tolerated, there were no effects on growth rate and also water and food intake were unchanged. At necropsy, no gross or microscopic pathological changes were found.

Groups of five male and five female young Sprague–Dawley rats were dosed with diets containing 0%, 0.17% (changed after 6 weeks to 0.5%) or 5% of MC (average intake equal to 690–775 mg/kg bw per day) for 8 months (Bauer and Lehmann, 1951). Group body weights and food and water consumption were recorded weekly. This treatment had no adverse effect on growth, but caused a significantly increased feed intake. Through 3 generations, reproduction was not impaired and the second and third generation rats dosed with 5% MC showed no adverse effects. A macroscopic and microscopic examination of representative animals revealed essentially normal tissues (not further specified). There also was no deposition of abnormal material in the tissues, indicating that no methyl cellulose was absorbed from the intestinal tract. After about 8 months on the experimental diet, the rats were mated. The young of the F1 and F2 generations were kept in groups of five and placed on 5% MC diet, and later mated in the same manner as the F0 generation. Representative animals from each group of the first generation were sacrificed at 8 months of age for macroscopic and microscopic examination. In the second experiment, nine young Sprague–Dawley rats (litter mates of the F1 generation, divided according to sex into three males and six females and weighing between 55 and 116 g), were placed on a modified paired-feeding regimen. This system was employed in order to determine the effect of massive dosage and the 'bulk' producing effects of the questionably inert substance, in contrast to one (cellulose flour) shown to be inert and to possess only a 'bulk' effect when included in the diet. The nine animals were divided into three groups. Rat 1 in each of the three groups received a diet of equal parts of the nutrient and of MC (50% MC diet) *ad libitum*. Rat 2 received a diet of equal parts of the nutrient and cellulose flour (forming the 'bulk' control) *ad libitum*, while rat 3 was given the nutrient alone (nutritive control). Each animal was housed in an individual metabolism cage, and daily records were kept of the urine volume, faeces weight and food and water consumption. Pooled 7-day urine samples from each rat were subjected to quantitative formic acid determinations. This study was terminated after 90 days of dosing. In dosed rats, growth depression was seen, but a subsequent replacement of MC or cellulose diet by the basal diet resulted in marked weight gain. There was no indication that significant amounts of MC were hydrolysed to cellulose and methanol in the intestinal tract.

In a long-term study, groups of 20 male and 20 female Wistar rats were dosed via diet containing 1 or 5% MC (15, 400 or 4,000 cP) (equivalent to 500 or 2,500 mg/kg bw per day) for 2 years (McCollister et al., 1973). Duplicate control groups consisted of 20 males and 20 females each. Additional groups of 10 rats of each sex for each treatment were set up for necropsy examination at 12 and 18 months. Haematological studies (PCV, Hb and total and differential WBC) were conducted at 12, 18 and 24 months on five male and five female rats from the groups fed the control ration and each of the 5% diets. All rats appeared normal and exhibited no unusual behaviour during the test period. Body weights were comparable between all groups and also feed consumption gave no compound-related differences. Mortality was unaffected by treatment and was associated with a variety of commonly observed spontaneous lesions. Haematological studies and determinations of BUN and AP gave normal findings, with no differences between control and treated rats indicative of a compound-related effect. Final mean body and organ weights of rats necropsied after 12, 18 and 24 months revealed a few random statistically significant differences, none of which was associated with treatment. Gross and histopathological examinations of the tissues showed no compound-related changes, nor any evidence to indicate storage of the test material within the cells of the reticula-endothelial system of treated rats. Also the observed tumours were similar in type and number in treated and control groups.

For obtaining data on tumour incidence from larger numbers of rats, diets identical to those fed in the above cited study as to sample and concentration were administered to groups of 30 male and 30 female Wistar rats for 2 years (McCollister et al., 1973). A control group of 30 rats of each sex received untreated diets. The rats were examined frequently for evidence of tumour development. Body weight records were maintained. Gross pathological examination was conducted on rats dying during the study or sacrificed in extremis, and sections of grossly visible nodules or masses were preserved for histopathological examination. Gross examination was conducted on all rats surviving at

the end of the 2 years. Weights of liver and kidneys were recorded and grossly evident lesions suggestive of tumour formation were preserved for histopathological examination. Also in this study, no adverse effects were seen concerning mortality, body weights, terminal liver and kidney weights or any increase in tumour incidences.

4.2.4.4. Ethyl cellulose (EC; E 462)

No data available.

4.2.4.5. Hydroxypropyl cellulose (HPC; E 463)

Rats

Groups of 10 young adult male and 10 female Wistar rats were administered daily doses of 0, 1,500, 3,000 or 6,000 mg/kg bw of HPC via gavage for 6 months (Kitagawa et al., 1976b). Rats were weighed every day and food consumption was measured twice a week during the study. The dosing caused a decrease in body weights of high-dosed male and female rats for 7–8 weeks (statistically significant for females). For the other investigated parameters (haematology, clinical chemistry and histopathology), no significant adverse findings were reported.

4.2.4.6. Hydroxypropyl methyl cellulose (HPMC; E 464)

Rats

In groups of 10 male and 10 female rats (strain not specified) dosed via diet with 0%, 20% or 25% of HPMC (equivalent to 0, 10,000 or 12,500 mg/kg bw per day) over 1 year, some retardation in growth was seen at a level of 20% (more pronounced at 25%). The dosing caused no increase in mortality and no adverse effects concerning urine analysis, haematology and histological examination were reported (Hodge et al., 1950).

In a 2-year study, four groups of 50 male and 50 female rats (strain not specified) were dosed via diet with 0%, 1%, 5% or 20% of HPMC (equivalent to 0, 500, 2,500 or 10,000 mg/kg bw per day) (Hodge et al., 1950). In males dosed with 20%, a slight retardation of body weight gain (about 30 g less compared to the other dose groups) was seen during the first year (weights taken weekly). During the second year (weights taken twice weekly), this trend was continued, although there were considerable fluctuations, especially near study termination. The mortality rates between all groups were comparable (60–84%). Pooled urine samples examined periodically for sugar and protein concentrations gave no changes. Also, a haematological examination (total erythrocytes, haemoglobin and total leucocytes) prior to beginning the study, eight times during the study, and at termination, gave no adverse effects. However, there was small decrease in RBC counts and Hb values in both sexes at a dose level of 20% (equivalent to 10,000 mg/kg bw per day), which was attributed to a nutritional origin. Organ weights recorded at autopsy were comparable between all groups and also a histological examination of stomach, small and large bowel, liver, kidneys, lungs, heart, brain, bladder, spleen, testes and bone marrow gave no indications for an adverse or a carcinogenic effect.

4.2.4.7. Ethyl methyl cellulose (EMC; E 465)

Mice

In an unpublished study, groups of 50 male and 50 female mice (strain not specified) were dosed via diet with 0%, 0.1% or 1% (equivalent to 0, 150 or 1,500 mg/kg bw per day) of EMC for 2 years. Apart from slightly decreased body weights in the latter part of the study seen in both sexes dosed with 1%, no adverse effects on survival rate, tumour incidence, blood picture and gross and microscopic appearance of internal organs were reported (ICI, 1966; cited in JECFA, 1990).

Rats

In a parallel study, groups of 50 male and 50 female rats (strain not specified) were dosed via diet with 0%, 0.1% or 1% (equivalent to 0, 50 or 500 mg/kg bw per day) of EMC for 2 years. Apart from decreased body weights in the latter part of the study seen in male rats dosed with 1%, no adverse effects on survival rate, tumour incidence, blood picture and gross and microscopic appearance of internal organs were reported (ICI, 1966; cited in JECFA, 1990).

4.2.4.8. Sodium carboxy methyl cellulose (NaCMC; E 466)

Mice

Groups of 50 male and 50 female young adult Alderley Park SPF mice were dosed via diet with 0, 10,000 or 100,000 mg/kg diet (equivalent to 0, 1,500 or 15,000 mg/kg bw per day) of sodium CMC for 100 weeks (McElligott and Hurst, 1968). In general, the dosing was well tolerated and caused no increased mortality in dosed mice. During the first 30 weeks, body weights and body weight gain were not affected, while thereafter, a retarded growth was noted in dosed mice. The final body weights at 0, 1,500 or 15,000 mg/kg bw per day were 45, 38 and 39 g for male mice and 39, 34 and 36 g for female mice. At necropsy, there was no histological evidence of changes in the intestinal wall indicating absorption of sodium CMC and also no evidence of storage in the regional lymph nodes or elsewhere. Also the tumour incidences were comparable among all groups.

CMC has been used as vehicle in a bioassay of selenium sulfide for possible carcinogenicity. Groups of 50 B6C3F1 mice of each sex were dosed via gavage with 10 mL/kg bw per day of 0.5% aqueous CMC (50 mg/kg bw per day) on 7 days per week for 103 weeks (NCI, 1980). Similar groups of untreated controls were also used. Observations made on the test animals were recorded twice daily. Examinations of animals for clinical signs and the presence of palpable masses were performed and recorded weekly. Mean body weights were recorded every 2 weeks for the first 12 weeks and then monthly for the remaining 93 weeks, with few exceptions. Animals that were moribund and those that survived to the termination of the study were killed and necropsied. Gross and microscopic examinations were performed on major tissues, major organs and all gross lesions from killed animals and from animals found dead. Compared with untreated controls, for all investigated parameters, no adverse effects were reported.

Rats

Ten male and 15 female young Wistar rats were fed a diet containing 5% CMC (equivalent to 2,500 mg/kg bw per day) for 201–250 days (Rowe et al., 1943). All animals were weighed twice weekly and individual weight records were kept throughout the experimental period. All the animals that were killed, as well as most of those that died during the study, were examined for gross pathology and lesions. The dosing had no adverse effects on growth rate, mortality and organ weights. Also, the results of histopathological examination of the liver, kidney, spleen, pancreas, adrenal gland, testis and GI tract showed no significant differences between the treated and the control groups.

Two groups of 50 male and 50 female white rats each were dosed with 500 or 1,000 mg/kg bw per day of CMC via diet for 6 months (Shelanski and Clark, 1948). Forty rats were used as controls. The animals were weight once monthly; other investigated parameters were fertility (not further specified), urine analysis (sugar, albumin and phosphates as well as microscopic examination for casts and blood cells), haematology at the beginning of the experiments, at the end of 3 months and at the end of 6 months (Hb percentage, leucocyte and erythrocyte counts as well as differential counts) and a histopathological examination in five rats from each dose group, as well as in three rats from the control group each month (liver, kidney, spleen, stomach, intestine and heart). For none of the investigated parameters were adverse effects reported.

CMC has been used as vehicle in a bioassay of selenium sulfide for possible carcinogenicity (NCI, 1980). Groups of 50 F344 rats of each sex were dosed via gavage with 1 mL/kg bw per day 0.5% aqueous CMC (5 mg/kg bw per day) on 7 days per week for 103 weeks. Similar groups of untreated controls were also used. Observations made on the test animals were recorded twice daily. Examinations of animals for clinical signs and the presence of palpable masses were performed and recorded weekly. Mean body weights were recorded every 2 weeks for the first 12 weeks and then monthly for the remaining 93 weeks, with few exceptions. Animals that were moribund and those that survived to the termination of the study were killed and necropsied. Gross and microscopic examinations were performed on major tissues, major organs and all gross lesions from killed animals and from animals found dead. Compared with untreated controls, for all investigated parameters, no adverse effects were reported.

Groups of 50 male and 50 female young adult Alderley Park SPF rats were dosed via diet with 0, 10,000 or 100,000 mg/kg diet (equivalent to 0, 500 or 5,000 mg/kg bw per day) of sodium CMC for 104 weeks (McElligott and Hurst, 1968). In general, the dosing was well tolerated and caused no increased mortality in dosed rats. During the first 30 weeks, body weights and body weight gain was not affected, while thereafter a retarded growth was noted in dosed rats. Although the feed intake was increased in dosed rats, the final body weights were dose dependently decreased (511, 498 and

451 g for male rats and 344, 337 and 287 g for female rats at 0, 10,000 or 100,000 mg/kg diet, respectively). Haematological examinations revealed no adverse effects. At necropsy, there was no histological evidence of changes in the intestinal wall indicating an absorption of sodium CMC and also no evidence of storage in the regional lymph nodes or elsewhere. Also the tumour incidences were comparable between all groups.

Four groups of 25 male and female white rats each were dosed via diet for over 2 years with 0, 100, 500 or 1,000 mg/kg bw per day of sodium CMC (Shelanski and Clark, 1948). The weight curves of the four groups were normal except that the groups receiving sodium CMC showed a slight increase in weight compared with control rats. Monthly urine (albumin, casts and sugar) and haematology examinations (Hb, RBC and WBC counts, differential counts) showed no deviations. Litters produced within all groups were kept in their respective groups and placed on the same diet as the parents. This was carried out into the third generation and these animals also showed no deviation from the animals in the control group. At the end of 25 months, 12 of the animals in each group were autopsied; no adverse findings were observed. Also a histological examination (heart, liver, kidney, stomach, intestine, spleen and adrenals) revealed no adverse findings.

Guinea pigs

Two groups of 50 male and 50 female guinea pigs each were dosed with 500 or 1,000 mg/kg bw per day of CMC via diet for 6 months (Shelanski and Clark, 1948). Forty guinea pigs were used as controls. The animals were weighted once monthly. Other investigated parameters were fertility (not further specified), urine analysis (sugar, albumin and phosphates, as well as microscopic examination for casts and blood cells), haematology at the beginning of the experiments, at the end of 3 months and at the end of 6 months (Hb percentage, leucocyte and erythrocyte counts, as well as differential counts) and a histopathological examination in five guinea pigs from each dosage group, as well as in three guinea pigs from the control group each month (liver, kidney, spleen, stomach, intestine and heart). For none of the investigated parameters were adverse effects reported.

In a one-year study, groups of 20 guinea pigs each were dosed with 500 or 1,000 mg/kg bw per day of CMC via diet (Shelanski and Clark, 1948). A control group consisted of 15 guinea pigs. Monthly weight records were kept and showed a similar body weight gain in all groups. All animals were autopsied at the end of the first year and none of the animals showed gross pathological changes. Also sections of liver, kidney, spleen, heart, stomach and intestines prepared from each animal and examined histologically showed no changes.

4.2.4.9. Cross-linked sodium carboxy methyl cellulose (E 468)

No data available.

4.2.4.10. Enzymatically hydrolysed carboxy methyl cellulose (E 469)

No data available.

4.2.4.11. Summary

Overall, in a chronic feeding study, no consistent effects on the body weight were reported even at very high doses of microcrystalline cellulose (30% in the diet) (Documentation provided to EFSA n. 40). Food efficiency, survival and haematology were comparable among all groups. The liver and kidney weights of males receiving microcrystalline cellulose gel were increased. Histopathology showed some dystrophic calcification of renal tubules in females of the high dose group. No further treatment-related changes were observed. Other available studies were less suitable for evaluation of this endpoint due to methodological shortcomings (Lewerenz et al., 1981a,b; Paulini et al., 1987) or limited reported information (Bieri et al., 1977; Nigro et al., 1979; Yartsev et al., 1989; cited in JECFA, 1990; Anastasia et al., 1990; Maurer et al., 1990). The Panel concluded that microcrystalline cellulose has no carcinogenic properties.

Data are available for methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, ethyl methyl cellulose and sodium carboxy methyl cellulose.

Groups of 20 male and 20 female Wistar rats were dosed via diet containing 1% or 5% (up to 5,000 mg/kg bw per day) methyl cellulose (15, 400 or 4,000 cP) for 2 years. For all examined parameters, no adverse effects were reported and also the observed tumours were similar in type and number in treated and control groups (McCollister et al., 1973). For obtaining data on tumour incidence from a larger number of rats, diets identical to those fed in the above cited study as to sample and concentration were administered to groups of 30 male and 30 female Wistar rats for 2

years. Also in this study, no adverse effects were seen concerning mortality, body weights, terminal liver and kidney weights or any increase in tumour incidences (McCollister et al., 1973).

In groups of 10 young adult male and female Wistar rats dosed daily via gavage with 0, 1,500, 3,000 or 6,000 mg/kg bw of hydroxypropyl cellulose for 6 months, apart from a decrease in body weights in high-dosed male and female rats, no other adverse effects were noted (Kitagawa et al., 1976b).

In an older study, groups of 50 male and 50 female rats (strain not specified) were dosed via diet with 0%, 1%, 5% or 20% of hydroxypropyl methyl cellulose (equivalent to 0, 500, 2,500 or 10,000 mg/kg bw per day). Also in this study, apart from a decrease in body weights of high-dosed males, no other significant adverse findings were reported and there was no indication of a carcinogenic effect (Hodge et al., 1950).

For ethyl methyl cellulose, data are available from two unpublished studies with rats and mice. In both trials, groups of 50 male and 50 female animals (strains not specified) were dosed via diet with 0%, 0.1% or 1% (equivalent to 0, 150 or 1,500 mg/kg bw per day for mice; equivalent to 0, 50 or 500 mg/kg bw per day for rats) over 2 years. Apart from decreased body weights in high-dosed animals, no adverse effects on survival rate, tumour incidence, blood picture and gross and microscopic appearance of internal organs were reported (ICI, 1966; cited in JECFA, 1990).

Sodium carboxy methyl cellulose was tested in two studies with groups of 50 male and 50 female Alderley Park SPF mice and Alderley Park SPF rats, respectively (McElligott and Hurst, 1968). The animals were dosed via diet with 0, 10,000 or 100,000 mg/kg diet (equivalent to 0, 1,500 or 15,000 mg/kg bw per day for mice; equivalent to 0, 500 or 5,000 mg/kg bw per day for rats) for up to 104 weeks. In the study with mice, during the first 30 weeks, body weights and body weight gain were not affected, while thereafter, a retarded growth was noted. The final body weights at 0, 10,000 or 100,000 mg/kg diet group were 45, 38 and 39 g for male mice and 39, 34 and 36 g for female mice. At necropsy, there was no histological evidence of changes in the intestinal wall indicating an absorption of the substance and there was also no evidence of storage in the regional lymph nodes or elsewhere. Also, the tumour incidences were comparable between all groups. In rats, during the first 30 weeks, body weights and body weight gain also were not affected, while thereafter a retarded growth was noted. Although the feed intake was increased in dosed rats, the final body weights were dose dependently decreased (511, 498 and 451 g for male rats and 344, 337 and 287 g for female rats at 0, 10,000 or 100,000 mg/kg diet, respectively). Also in this study, there was no evidence of histological changes in the intestinal wall indicating absorption of sodium carboxy methyl cellulose and also no evidence of storage in the regional lymph nodes or elsewhere. The tumour incidences were comparable among all groups.

4.2.5. Reproductive and developmental toxicity

4.2.5.1. Microcrystalline cellulose (E 460(i))

Reproductive toxicity studies

Rats

In a report available from secondary source (Documentation provided to EFSA n. 41), groups of eight male and 16 female rats were used to produce P, F1a, F1b, F2 and F3 generations after having been fed on diets containing 30% microcrystalline cellulose flour or gel (equivalent to 15,000 mg/kg bw per day). The control received 30% 'ordinary cellulose' (no further details). The authors stated that no adverse effects on reproduction and no developmental effects were seen. The evaluation of this study is hampered by limited and inconsistent documentation.

An unpublished, combined, one-generation reproduction/chronic toxicity study in rats with microcrystalline cellulose (90% of particles < 20 μm) in the diet at levels of 0 (control), 30, 100 or 200 g/kg diet (equivalent to 0, 1,500, 5,000 or 10,000 mg/kg bw per day) (Lewerenz et al., 1979, 1981a; referred to by SCF, 1999) revealed no effects on reproductive parameters (no details reported). Due to the limited reporting and low number of animals involved, the Panel considered this study inadequate for risk assessment.

Developmental toxicity studies

Rats

Groups of 25 pregnant Sprague–Dawley rats received Avicel® RCN-15 (a mixture of 85% microcrystalline cellulose with 15% guar gum; median particle size of 21 μm, only 1% of particles < 5 μm) in the diet at dose levels of 0%, 2.5% or 5.0% (equal to 0, 2,091 or 4,490 mg/kg bw per day)

ad libitum on gestation day (GD) 6–15 (Freeman, 1992b). Animals were fed basal diet at all other times. The treatment in the high-dose group resulted in a significant increase in food consumption from GD 6 to 15, presumably due to the increased fibre content. On GD 20, a caesarean section was performed. Number and distribution of corpora lutea, implantation sites, early and late resorptions, live and dead fetuses and fetal sex were determined. External, visceral and skeletal examinations of the fetuses were performed. There was no evidence for maternal toxicity or any developmental effects of microcrystalline cellulose. The NOAEL for maternal and developmental toxicity was 4,500 mg/kg bw per day.

In a second study, the same experimental design was used, but pregnant rats were exposed to Avicel® CL-611, a mixture of 85% microcrystalline cellulose and 15% sodium carboxy methyl cellulose Documentation provided to EFSA n. 33). The mean particle size was 32 μm (1% of particles < 5 μm). The doses were of 0%, 2.5% or 5.0% (equal to 0, 2,207 and 4,584 mg/kg bw per day), respectively. In this study, the food consumption was significantly increased at the 2.5% and 5% level. There was no evidence for maternal toxicity or any developmental effects of microcrystalline cellulose. The NOAEL for maternal and developmental toxicity was 4,600 mg/kg bw per day.

4.2.5.2. Powdered cellulose (E 460(ii))

Reproductive toxicity studies

Mice and rats

The effects of a synthetic diet (AIN-76™) containing 5% cellulose (no further details) (equivalent to 2,500 mg/kg bw per day) for 6 weeks prior to mating and during pregnancy and lactation were compared with a control group receiving a cereal-based diet containing 4.5% crude fibre (no further details) in rats and mice (strains not specified) (Bieri et al., 1977). In each group, 7–8 pregnant rats were used (no further details). Litter size, birth weight, number of weaned F1 rats and body weight of weaned rats were measured. In a first trial, no differences were found between controls and treated rats. In an independent second experiment, birth weight and body weight at weaning were significantly increased in treated rats. No effects on reproduction and lactation were detected in similar experiments with mice. The reporting and the parameters measured were very limited.

Developmental toxicity studies

Rats

Four groups of 9–12 pregnant Sprague–Dawley rats were fed at GD 6–15 a mixture of four types of α-cellulose (Elcema®; four types of α-cellulose in the ratio of 1/1/1/1: particle size 1–50 μm (powder), 1–100 μm (powder), 1–150 μm (fibrillar), 90–250 μm (granulate)) at dose levels of 0%, 2.5%, 5% or 10% in the diet (equivalent to 0, 1,250, 2,500 or 5,000 mg/kg bw per day) (Ferch, 1973a,b, 1974). Maternal weight was measured every third day and dams were killed on day 21 of pregnancy for caesarean section. Number, sex and weight of fetuses, corpora lutea, early and late resorption, litter size and average backbone length were determined. Fetuses were examined for external malformations, soft tissue or skeletal defects. Additionally, two groups of pregnant rats received at GD 6–15 the basal diet (n = 12) or 10% cellulose in the diet (n = 10) and dams were allowed to deliver the pups, which were maintained to weaning (day 21 postnatal). In these additional groups, the following parameters were measured: duration of pregnancy, number of pups born and surviving postnatal period, and weight of pups at days 7 and 21; pups were killed at day 21 postnatal and histopathology was performed. Presumably basal diet was fed at all other times in both trials. No statistical analysis was performed. The treatment did not induce effects on maternal weight gain. There were no altered parameters after the caesarean section in comparison to the concurrent control, except for a slight, but not dose dependent, increase in early resorptions (limited reporting prevents the evaluation of this effect). However, the authors stated that no effects on early resorptions were noted in comparison to historical controls. The treatment with 10% cellulose did not affect postnatal development. The Panel noted that the test substance was not compliant with the specifications of the food additive.

4.2.5.3. Methyl cellulose (MC; E 461)

Reproductive toxicity studies

No studies available.

Developmental toxicity studies

Mice

Groups of 20–22 pregnant albino CD-1 outbred mice were dosed once daily via gavage with 0, 16, 74, 345 or 1,600 mg/kg bw per day of a MC (FDA 71-51) suspension in corn oil (dose volume 10 mL/kg bw) from GD 6 to 15. The control group received daily doses of corn oil. A caesarean section was performed on GD 17. In dams dosed with 1,600 mg/kg bw per day, a significant increase in mortality was observed, with a reduced rate of pregnancy in survivors. At term, resorption sites were markedly increased in number, live fetuses were significantly reduced in number and fetal weight decreased. At external and visceral examination of the fetuses, no dose-related abnormalities were observed. At fetal skeletal examination, the ossification of the fetuses was retarded in the 1,600 mg/kg bw group. In fetuses, there was no evidence for developmental effects at any dose level (FDLI, 1973; cited in JECFA, 1990).

Groups of 12–17 pregnant mice (CD/1 strain) were dosed once daily via gavage with 0, 70, 153, 330 or 700 mg/kg bw per day of a MC (FDA 71-51) suspension in corn oil (dose volume 5.8, 12.7, 27.5 or 58.3 mL/kg bw) from GD 6 to 15. The control group received corn oil at the same dose as the highest dose. A caesarean section was performed on GD 17. There were no dose-related effects on growth, mortality or incidences of gross lesions in dams and in the number of implantations, resorptions, live and dead fetuses and fetal weight. No increase in incidences of external, visceral and skeletal abnormalities, reduced weight, or mortality was observed in fetuses from treated dams (Cannon Labs, 1975; cited in JECFA, 1990).

Rats

Groups of 20–25 pregnant rats (not further specified) were dosed once daily via gavage with 0, 13, 51, 285 or 1,320 mg/kg bw per day of a MC suspension in corn oil (dose volume 6, 1, 1, 2 or 6 mL/kg bw) from GD 6 to 15. The control group received daily doses of corn oil. A Caesarean section was performed on GD 20. In dams dosed with 1,320 mg/kg bw per day, a reduced pregnancy rate was observed. The dosing gave no adverse effects on growth, mortality or incidence of gross lesions in dams. Also, the incidences of implantations, live or dead fetuses and resorptions were not affected. Apart from an increased incidence of extra centres of ossification in vertebrae of fetuses from high dose dams, no increase in incidences of external, visceral and skeletal abnormalities was observed in fetuses. Also, fetal weights were not affected (FDLI, 1973).

Groups of 13–19 pregnant Sprague–Dawley rats were dosed once daily via gavage with 0, 120, 260, 550 or 1,200 mg/kg bw per day of a MC suspension in corn oil (dose volume 12, 1.2, 2.6, 5.6 or 12 mL/kg bw) from GD 6 to 15. The control group received daily doses of corn oil. A Caesarean section was performed on GD 20. There were no dose-related effects on growth, mortality or incidence of gross lesions in dams. The incidences of implantations, live fetuses, corpora lutea, dead fetuses and resorptions in treated dams were within the normal range. Apart from a slight increased incidence of extra centres of ossification in vertebrae of fetuses from the high-dose group, no increase in incidences of external, visceral and skeletal abnormalities was observed in fetuses. Also, fetal weights were not affected (Cannon Labs, 1977).

Hamsters

Groups of 22–24 Golden hamsters were dosed once daily via gavage with 0, 46, 216 or 1,000 mg/kg bw per day of a MC suspension in corn oil (dose volume 4, 1, 1 or 4 mL/kg bw) from GD 6 to 10. The control group received daily doses of corn oil (negative control). A caesarean section was performed on GD 14. There were no dose-related effects on growth, mortality or incidences of gross lesions in dams. Also, the incidences of implantations, live and dead fetuses and resorptions in dams were within the normal range. In fetuses, there were no increased incidences of external, visceral and skeletal abnormalities and also fetal weights were not affected (FDLI, 1973).

Rabbits

Groups of 10–17 Dutch belted rabbits were dosed once daily via gavage with 0, 7, 32, 148 or 685 mg/kg bw per day of a MC suspension in corn oil (dose volume 3, 1, 1, 1 or 3 mL/kg bw) from GD 6 to 18. The control group received daily doses of corn oil (negative control). A Caesarean section was performed on GD 29. Dams of the highest dose group showed an increased mortality and a decrease in pregnancy rate in survivors, but no dose-related effects on growth or incidence of gross lesions. The incidences of corpora lutea, implantations, live and dead fetuses and resorptions in dams were within

the normal range. In fetuses, there were no increased incidences of external, visceral and skeletal abnormalities and also fetal weights were not affected (FDLI, 1973). Due to the high mortality in the high-dose group, the Panel considered this study not relevant for risk assessment.

4.2.5.4. Ethyl cellulose (EC; E 462)

Reproductive and developmental toxicity studies

No studies available.

4.2.5.5. Hydroxypropyl cellulose (HPC; E 463)

Reproductive toxicity studies

No studies available.

Developmental toxicity studies

Rats

Pregnant Wistar rats (JCL) were dosed via gavage from GD 7 to 17 with 0, 200, 1,000 or 5,000 mg/kg bw hydroxypropyl cellulose of low substitution (L-HPC) (Kitagawa et al., 1978a). Since L-HPC is insoluble in water, 8 g were suspended in 100 mL of 1% gum arabic solution. The amounts of suspension administered were 2.5, 12.5 or 62.5 mL/kg bw in the low-, mid- and high-dose group. The control group received 62.5 mL/kg bw of 1% gum arabic solution. The group sizes were 21–24 animals for caesarean section and 12–15 animals for spontaneous delivery. During the gestation period, general symptoms, mortality and abortion rates of dams were examined. Body weight, and food and water intake were recorded every 3 days. On GD 21, 21–24 pregnant females in each group were necropsied by caesarean section. The number of corpora lutea, implantations, viable and dead fetuses, and resorbed embryos were counted, and positions of implantations were observed. Body weight of all viable fetuses were weighed individually and examined for external abnormalities and gender. Two to three of the viable fetuses per litter (random) were stained with alizarin Red S and examined for skeletal anomalies and development. The other fetuses were examined for visceral abnormalities. In the control, low-, mid- and high-dose groups, litter weight (36.6, 34.4, 33.8 and 28.4 g) and the percentage of pre-implantation loss (14.9%, 11.1%, 14.75 and 24.4%) and post-implantation loss (6.2%, 6.5%, 10.2%, and 13.5%) were significantly increased in the high-dose group. The number of live fetuses in the control, low-, mid- and high-dose groups was 9.0, 9.0, 8.8 and 7.5. The authors considered the effect in the high-dose group not as treatment-related, as this effect (pre-implantation loss) occurred before administration of the test substance. Furthermore, no decrease in the number of liveborn pups was observed in the dams which were allowed to litter. Furthermore, these effects were not observed in the litters of dams which were allowed to deliver. The Panel agreed with the authors.

Twelve to 15 dams in each group of the study described above were allowed to deliver spontaneously (Kitagawa et al., 1978a). Condition of each delivery was observed and the number of viable and stillborn pups was counted. Body weight, sex and external anomalies were examined. Litters were not adjusted. During the lactation period, general behaviour of the dam and newborn were observed, and at the third day after birth and once a week thereafter, food consumption and body weight gain of pups were recorded. The body weight of each newborn was weighed individually at the time of birth and weaning. Otherwise, the body weight was recorded as 'litter weight' by weighing a whole litter of each dam. Incisors eruption and eye opening were recorded. Pups were weaned at the 28th day of birth and dams were dissected. On the 35th day, each weanling rat was examined for the general behaviour and nervous functions, including anomalies in general behaviour, righting reflex, corneal reflex, pinna reflex, body posture, traction and responsiveness to sounds. All of the weanling rats from each litter were examined for skeletal anomalies taking soft X-ray pictures, except for two males and two females randomly selected. Each was then dissected for the examination of visceral malformations and positioning. One male and one female from each litter were sacrificed and wet weights of brain, heart, lung, liver, spleen, kidney, thymus, adrenal, testis epididymis, prostate gland, ovary, pituitary gland and thyroid gland were weighed. The weaning ratio was calculated conventionally from the data obtained at 3 weeks. Offspring (F1) grown over 5 weeks were examined for weight gains. After maturity, conditioned avoidance test and reproductive ability were examined. For the reproductive ability, F1 offspring (42 from the 200 mg/kg bw group, 56 from the 1,000 mg/kg bw group and 52 from the 5,000 mg/kg bw group) were used. Each male was examined for descent

of testis at an age of 4 weeks, and each female was examined for opening of vagina at the age of 5 weeks. At weeks 10–11 (about 1 week prior to mating), the oestrus cycle of each female was examined, and in week 11–12, each male and female among the same group were housed together and observed for mating. The mating period was 15 days and during this period, oestrus cycle of each female was examined every day until mating was confirmed. Each male and female was separated after the confirmation of mating and the body weight of each female was recorded daily until GD 21. On GD 21, a caesarean section was performed in each female, and implantations, corpora lutea, viable or non-viable fetuses and the weight of each fetus were recorded, as well as external anomalies of each fetus. In this part of the study, no effects on the number of pups, pup survival, growth and physical development and reproduction (parameters) were observed. The authors considered *in utero* exposure to the highest dose of 5,000 mg/kg bw per day as the NOAEL for this study and the Panel agreed with this conclusion.

Developmental toxicity studies

Rabbits

In a study with Himalayan rabbits, groups of 11–12 pregnant animals were dosed daily via gavage with 0, 200, 1,000 or 5,000 mg/kg bw of HPC during GD 6–18 (Kitagawa et al., 1978b). The test substance was suspended in 1% arabic gum solution. The dose volume in the control, low-, mid- and high-dose group was 50, 10, 10, or 50 mL/kg bw. Caesarean sections were performed on GD 29 and all fetuses were examined for skeletal and organ malformations. In high-dose dams, a slight body weight loss was seen up to GD 18. In the mid-dose group, the resorption rate was significantly increased (3.4%, 6.1%, 27.4% and 7.4%). The mean number of viable fetuses in the control, low-, mid-, and high-dose group was 7.0, 5.5, 4.8 and 5.7 (historical control 6.37). Mean fetal viable weights were comparable between the different groups. In high-dose dams, the pre-implantation loss was significantly increased (13.6%, 22.4%, 17.0% and 29.2%). The treatment gave no indications for an increased incidence of malformations. The Panel noted that from this study no NOAEL can be derived, as the number of fetuses was low in all dose groups.

4.2.5.6. Hydroxypropyl methyl cellulose (HPMC; E 464)

No studies available.

4.2.5.7. Ethyl methyl cellulose (EMC; E 465)

Reproductive and developmental toxicity studies

No studies available.

4.2.5.8. Sodium carboxy methyl cellulose (NaCMC; E 466)

Reproductive toxicity studies

Rats

In a study with male and female Sprague–Dawley-derived rats, 20 male and 40 female rats were dosed via gavage with 0 or 200 mg/kg bw per day of CMC (aqueous solution, dose volume 10 mL/kg bw) for at least 60 days (males) or for least 14 days (females) prior to mating, and also during the 6-day mating period (Fritz and Becker, 1981). One half of the females were dosed until sacrifice on GD 14, while the other half was dosed until weaning of the progeny (day 28 after birth). The treatment caused no adverse reactions in the parents and also average body weights were comparable throughout the study. In dams, no adverse effects concerning mating efficiency, pregnancy rate, mean numbers of corpora lutea and implantation sites, ratios of corpora lutea to implantation sites or resorption rates were noted. For the offspring, there were also no significant changes in litter sizes, sex ratios, body weight gains, nesting behaviour, eye opening and pinna detachment. In addition, behavioural testing (e.g. righting and direct pupillary reflex) gave no adverse effects. Data were not described very detailed in the publication. The only dose tested (200 mg/kg bw per day) did not induce effects with regards to parental toxicity, reproduction and development and behaviour of the offspring.

Developmental toxicity studies

Mice

In a study with pregnant albino CD-1 outbred mice, groups of 19–24 animals were dosed via gavage with 0, 16, 74, 345 or 1,600 mg/kg bw per day of sodium CMC in corn oil (dose volume 10

mL/kg bw per day) from GD 15. The treatment caused no mortality, and no adverse effects were observed on implantation or on fetal survival. There was also no increase in abnormalities of soft or skeletal tissues compared with non-dosed controls (FDLI, 1975).

Rats

In another study with pregnant Wistar-derived rats, groups of 19–22 animals were dosed via gavage with 0, 16, 74, 345 or 1,600 mg/kg bw per day of sodium CMC in corn oil (dose volume 5, 1, 1, 2 or 5 mL/kg bw) from GD 6 to 15. The treatment caused no mortality, and no adverse effects were observed on implantation or on fetal survival. There was also no increase in abnormalities of soft or skeletal tissues compared with non-dosed controls (FDLI, 1975).

4.2.5.9. Cross-linked sodium carboxy methyl cellulose (E 468)

Developmental studies

Rats

Cross-linked sodium carboxy methyl cellulose was administered to pregnant Sprague–Dawley CD rats (25 females; age not stated) at 0, 10,000 or 50,000 mg/kg diet *ad libitum* from GD 6 to 15 (equal to 0, 910 or 4,554 mg/kg bw per day) (Freeman et al., 2003). During GD 0–6 and GD 15–20, the animals received an untreated basal diet, which was also given to the control animals for the duration of the experiment. The animals were observed daily with detailed assessment of test material-related effects. Body weight and food consumption were recorded. Clinical examinations included recording the onset and duration of any toxicological effects. On GD 20, the animals were terminated, and all dams examined for gross lesions, implantation sites, late resorptions and status of fetuses and corpora lutea. The fetuses were examined for external alterations, after which they were euthanised, and visceral and skeletal examinations carried out to detect abnormalities. No treatment-related clinical signs or deaths were reported in the study. There were also no effects on body weight, uterine weights or food consumption in dams compared to controls. No effects were noted in dams during necropsy, and there were no external, skeletal or visceral malformations in the fetuses. The study authors concluded that there were no treatment-related statistically significant findings in the developmental study. The Panel agreed with this conclusion and considered 4,554 mg/kg bw per day as the NOAEL for this study.

4.2.5.10. Enzymatically hydrolysed carboxy methyl cellulose (E 469)

No data available.

4.2.5.11. Summary

Data from dietary reproductive studies were available for microcrystalline cellulose, powdered cellulose and sodium carboxy methyl cellulose, (Documentation provided to EFSA n. 41, Lewerenz et al., 1979; referred to by SCF, 1999; Bieri et al., 1977; Fritz and Becker, 1981).

Several prenatal developmental studies with oral dosing via diet of microcrystalline cellulose, powdered cellulose and via oral gavage of methyl cellulose, hydroxypropyl cellulose, sodium carboxy methyl cellulose and cross-linked sodium carboxy methyl cellulose have been performed in mice, rats, hamsters and/or rabbits (FDLI, 1973, 1975; Cannon Labs, 1975, 1977; Kitagawa et al., 1978a,b; Fritz and Becker, 1981; Freeman, 1992b).

From these studies, it can be concluded that adverse effects on reproduction and development were unlikely.

- The reproductive toxicity studies with **microcrystalline cellulose** and **powdered cellulose** did not report adverse effects up to 15,000 and 7,500 mg/kg bw per day, respectively. However, the Panel noted that the studies were limited in design and reporting. In prenatal developmental toxicity studies in rats, doses up to 10% powdered cellulose in the diet (equivalent to 5,000 mg/kg bw per day) did not induce maternal or developmental toxicity and did not affect postnatal development (FDLI, 1973; Ferch, 1973a,b, 1974; Cannon Labs, 1975; Freeman, 1992b).
- From prenatal developmental toxicity studies by gavage in mice, rats and golden hamsters, the Panel derived a NOAEL of 700, 550 and 1,000 mg **methyl cellulose**/kg bw per day, respectively (vehicle: corn oil, daily dosing from GD 6 to 15) (FDLI, 1973; Cannon Labs, 1977).

- In rats, no treatment-related developmental effects were observed at 5,000 mg **hydroxy propyl cellulose**/kg bw per day, the highest dose tested (Kitagawa et al., 1978a). Himalayan rabbits dosed daily by gavage with 0, 200, 1,000 or 5,000 mg **hydroxypropyl cellulose**/kg bw per day (Kitagawa et al., 1978a) showed a decreased number of viable fetuses in all treated groups. Therefore, the Panel could not derive a NOAEL from this study.
- Besides the reproductive study with a single dose, in which no reproductive effects were observed, a prenatal developmental toxicity study in mice and in rats was performed with **sodium carboxy methyl cellulose**. In mice and rats, no effects on maternal or developmental toxicity were observed after daily dosing up to 1,600 mg **sodium carboxy methyl cellulose**/kg bw per day by gavage (vehicle: corn oil, daily dosing from GD 6 to 15) (FDLI, 1975).
- **Cross-linked sodium carboxy methyl cellulose**, when fed in the diet in a prenatal developmental toxicity study at doses equal to 910 or 4,554 mg/kg bw per day from GD 6 to 15 to rats, gave no effects on maternal or developmental toxicity (Freeman et al., 2003). The NOAEL of this study was 4,554 mg/kg bw per day.

4.2.6. Hypersensitivity, allergenicity and food intolerance

In the JECFA evaluation (1998), the Committee stated that microcrystalline cellulose had no skin sensitising properties in guinea pigs (Freeman, 1991; referred to by JECFA, 1998a,b, 1999a,b) (Freeman, 1996b; referred to by JECFA, 1998a,b, 1999a,b).

In human subjects suffering from seasonal allergic rhinitis, inhalation of inert cellulose powder or oxidised cellulose has been reported to improve hay fever symptoms (Josling and Steadman, 2003; Shani et al., 2011). However, this was not confirmed in other studies where the authors concluded that microcrystalline cellulose did not prove to be significantly better than placebo in treating seasonal allergic rhinitis symptoms (Paz Lanberg et al., 2016).

Anaphylactic reactions to carboxy methyl cellulose have been rarely reported (Dumond et al., 2009) and this was usually when the cellulose was injected. Two patients who presented that reaction, did not react to orally administered CMC (Rival-Tringali et al., 2008).

Overall, the Panel considered that there is no indication for an hypersensitivity potential for celluloses (E 460–466, E 468–469) used as food additives.

4.2.7. Other studies

4.2.7.1. Human studies

Microcrystalline cellulose

In patients given 30 g microcrystalline cellulose per day as dry flour (one male) or gel (one female) for 5 weeks (added to the free-choice diet), no significant effects in the GI tract were noted during the administration period (Tusing, 1964).

Microcrystalline cellulose was used in the treatment of constipation in obese patients. After recording control values for body weight, body mass index, total and fractionated cholesterol, triglycerides, A and B lipoproteins, uric acid, glucose and glycosylated haemoglobin, a group of 30 subjects received for 4 weeks 2.4 g microcrystalline cellulose in tablet form in the morning and 3.6 g in the evening (Adamii et al., 1998). In a further trial using the same experimental design, 10 obese subjects were treated for 8 weeks and additionally blood counts and plasma iron levels were determined. Each subject stated in a questionnaire data about evacuations and clinical symptoms. No adverse effects were reported. Improved defecation was observed in 83% of the patients in the first trial and in 9 out of 10 subjects in the second trial. No changes were found in controlled parameters.

In an unpublished clinical study (data from secondary source), eight male and eight female volunteers supplemented for 6 weeks their diet with 30 g microcrystalline cellulose per day as either dry powder or gel (15% aqueous) (Documentation provided to EFSA n. 39. The treatment period followed 2 weeks without supplementation. No adverse findings were reported on body weight. Most subjects complained of fullness and mild constipation. Haematology was normal in all subjects and clinical chemistry showed no differences between treatment and control periods. There was no evidence for effects on liver or kidney function; urinalysis produced normal findings. Analysis of faeces revealed no effects on faecal flora but the amount of cellulose in faeces increased 5–8 eight times during the test period. Microscopy revealed the presence of microcrystalline cellulose in faeces.

The effects of microcrystalline cellulose were compared in a double-blind, cross-over trial in 20 poorly controlled Type 2 diabetic patients (initially 16 women and six men; ages ranged from 40 to 76 years, mean 63 years) (Niemi et al., 1988). There were 12-week control and treatment periods separated by a 4-week wash-out period. Cellulose was given at 15 g/day for a 2-week period and then at 5 g/day for the remaining 10-week period. Parameters in the control and treatment period were measured after 6 and 12 weeks. Questionnaire survey was performed by physicians. Four patients reported mild flatulence or loose stools during the treatment. There was no significant change in body weight and blood pressure. Serum zinc, ferritin or urinary magnesium excretion were not altered during the treatment period. There was no effect on fasting blood glucose level, glycosylated haemoglobin, serum high density lipoprotein cholesterol and serum triglycerides.

No change was noted in blood chemistry parameters in eight healthy male volunteers after daily ingestion of 30 g microcrystalline cellulose as supplement to their diet for 15 days (limited information, data from secondary source) (Asahi Chemical Industry Co., 1966; referred to by JECFA, 1998a,b, 1999a,b). Furthermore, faecal flora did not show any alterations. The absorption of I^{131}-triolein was unaffected, and examination of urine, blood and faecal levels of vitamin B1 during treatment showed no difference from control periods. D-xylose absorption was lower during microcrystalline cellulose ingestion.

In 11 healthy female volunteers (19–22 years old), the post-prandial serum vitamin A concentration was measured 3, 5, 7 and 9 h after oral administration of 300,000 IU vitamin A-palmitate given with a formula diet, to which 0 or 40 g microcrystalline cellulose (no further details) were added (Kasper et al., 1979). The areas under the serum vitamin A concentration curves were significantly increased, suggesting an increased amount of vitamin A being absorbed.

A group of 12 female volunteers (non-pregnant, not lactating; no further data) received 5 g microcrystalline cellulose in 200 mL water containing 15 g sucrose and 3 mg radiolabelled Fe as iron sulfate. Controls (n = 12) received the same amount of Fe in a jelly containing 5 g pectin. Microcrystalline cellulose did not appear to inhibit the uptake of iron (Gillooly et al., 1984).

Three men received 10 g of cellulose in addition to a low-fibre diet for 20-day (Ismail-Beigi et al., 1977). The faecal excretion of zinc and calcium was increased. The magnesium balance became negative in two subjects and the phosphorus balance negative in one subject. When cellulose was added to a fibre-rich diet, faecal excretion of calcium and zinc increased in two subjects and magnesium in one.

α-Cellulose and unspecified celluloses

Bradlow et al. (1994) tested α-cellulose in a clinical study. Using a randomised clinical trial, groups of 20 female volunteers received daily for 3 months 20 g packets of α-cellulose (women aged 27–48 years, mean body weight 59 kg) or a placebo (aged 18–53 years, mean body weight 57 kg). The packets were mixed with fruit juice. Urine and blood samples were collected at the end of each month. Haemoglobin, platelets, several clinical chemistry and endocrinological parameters were determined. The urinary 2-OH-oestrone:oestriol oestrogen metabolite ratio was measured monthly at the same time of the menstrual cycle. In most subjects, the cellulose was well tolerated; a few subjects dropped out of treatment group because they found the cellulose suspension very unpleasant to consume (no details about final group number). No other unpleasant symptoms or problems were reported in the questionnaire. No differences between control and treatment group were observed in any parameter examined.

A cross-over design study (two periods of 4 weeks) in a group of 10 healthy volunteers (six women and four men; mean age 24 years) was undertaken to determine the effects of daily dietary supplementation with 15 g/day α-cellulose fibre (99.5% pure; derived from wood; Sigma Chemical Comp.) (Hillman et al., 1985) on serum lipid levels. There was no significant change in dietary intakes except for the fibre supplement. Each subject acted as his/her own control. At the end of both the control and test periods, fasting blood sample were taken. Cellulose did not alter serum total cholesterol, triglycerides, high-density lipoprotein cholesterol, or the ratio of high-density lipoprotein to total cholesterol.

Seven healthy women consumed a low-fibre diet of constant composition and the same metabolically controlled diet, to which 16 g of refined cellulose (Solca Floc, 85% wood α-cellulose and 15% non-glucose hemicelluose) was added for 30 days (Slavin and Marlett, 1980). After cellulose consumption, the mean daily wet stool weight, main dry stool weight and the frequency of defecation were increased. Cellulose shortened the transit time. Faecal excretion of calcium and magnesium were increased after cellulose consumption.

The effects of 21 g pure cellulose added to a low-fibre diet were tested in nine non-anaemic adolescent girls (age 16–18 years, average weight and height 48 kg and 155 cm) (Godara et al., 1981). The girls consumed first a low-fibre diet for 21 days and thereafter the high-fibre diet. The cellulose intake increased the faecal excretion of calcium, phosphorus and the serum levels of calcium, inorganic phosphorus and iron were decreased.

King et al. (1982) reported no effects on daily excretion of zinc, copper, calcium and magnesium after feeding cellulose (0.5 g/kg bw per day) to 5 young men for 9 days in an egg white protein formula. Faecal iron was increased in the cellulose group. Another group (n = 5) was fed for 15 days egg white protein formula to which cellulose (0.5 g/kg bw per day) or phytate (3 g/day) was added. The phytate diet did not increase the faecal dry solids but the faecal excretion of calcium, magnesium and zinc in this group was increased. Serum calcium, magnesium and zinc did not change with the phytate feeding. According to the authors, the alteration in absorption of calcium, magnesium and zinc is due to phytate and not to the fibre components.

After intake of 15 g cellulose/day for 4 weeks by 5 males and 5 females (age 21–26 year), the effects on stool pH, transit time and weight were measured (Hillman et al., 1983). In females, nausea, retching (n = 1) and cramps and urgency (n = 1) were reported. The stool pH was decreased, the stool transit time decreased and the stool weight increased.

The effects of 14 g/day of purified cellulose (99% cellulose on a dry basis) for 24 days was studied in 13 healthy male and female adults (age 23–60 years) (Spiller et al., 1980). The subjects were chosen on the basis of slow intestinal transit time and low faecal output when consuming their normal diets. Faecal weight increased and the transit time decreased. During the study, the faecal volatile fatty acids concentration did not change.

Methyl cellulose (MC; E 461)

In three healthy adults, 5 g of methyl cellulose (4,000 cP) given twice daily over 8 days both increased the number of stools per day and also the volume of the stools about twofold (Tainter, 1943).

In an older study, it was reported that the intake of 2.5–5.25 g of MC taken orally as gel was mildly constipating (Bauer, 1945).

In 29 and in 8 patients suffering from acute and/or chronic constipation, the daily uptake of 1–3 g of MC over 3–180 days or the daily uptake of 6 g over 4–240 days caused a significant relief and was well tolerated without toxicity (Schweig, 1948).

In six patients suffering from irritable bowel associated with diarrhoea or constipation, the oral uptake of 2 g of MC every 4 h resulted in abdominal comfort and the reduction of number of stools (Bargen, 1949).

In two female patients with an age of 31 and 35 years, after an oral uptake of 60–90 mL of a short-chain MC preparation daily over 5 days, symptoms such as generalised oedema, mental cloudiness, and poor coordination of some skeletal muscle actions were observed, which disappeared within 72 h of cessation of intake. During administration, sodium and water retention, increase in serum osmolality and an up to 75% decrease in urinary aldosterone excretion were seen (Crane et al., 1969).

In an unpublished study, five adult male volunteers were given daily doses of 250 mg/kg bw of MC, divided into three equal portions, over a period of 23 consecutive days. The treatment was well tolerated and gave no allergic responses or alteration in normal elimination patterns. MC administered as a prehydrated gel caused increased faecal weights (wet and dry basis), but had variable effects on intestinal transit time, causing increased transit time in three subjects and decreased transit time in the other two. Haematology, serum biochemistry and urinalysis parameters were within normal limits. Small, but significant, reductions were observed in faecal volatile fatty acids and neutral sterols, but breath hydrogen levels were not affected (Eastwood et al., 1988, 1990).

In a study with 50 healthy adults (44 women and six men with an age of 18–70 years), the subjects were dosed with 19 g of a placebo during the first week (Hamilton et al., 1988). Then each of the subjects was randomised to 1 of 3 arms: a second week of a daily dose of 19 g of placebo, or 19 g of the bulk laxative containing 2 g MC, or 38 g of the laxative containing 4 g of MC. Nine subjects completed the protocol on placebo, 20 subjects on 2 g MC and 21 on 4 g MC. At the end of the study, stools were analysed for faecal weight, faecal solids, water content and percentage of water. In a second phase of the study, during the first week of the protocol, all subjects (135 women and 14 men with an age of 18–70 years) took the 19 g of placebo. The second part of this protocol was a 10-day treatment period during which the subjects were randomised into one of four daily dosage groups: the study bulk laxative containing 1, 2 or 4 g MC in a total weight of 9.5, 19 or 38 g, respectively, or a similar-appearing preparation, 11 g in weight, containing 3.4 g of psyllium as positive control. Only 59

subjects (56 women, three men) entered into the second part of phase 2 (15 on 3.4 g psyllium, 15 on 1 g MC, 15 on 2 g MC and 14 on 4 g MC). The age range of this group was 19–59 years. As in phase 1, stools were analysed for total weight, faecal solids, total water content and percentage water. MC in daily doses of 4 g caused a statistically significant increase in faecal frequency, faecal water and faecal solids. The results of the second phase showed that the dosing with MC statistically significantly increased stool frequency, water content and faecal solids.

Ethyl cellulose (EC; E 462)

No data available.

Hydroxypropyl cellulose (HPC; E 463)

In a clinical trial, patients (aged 18 years or more) with chronic watery diarrhoea, presumably secondary to idiopathic bile acid malabsorption, were randomly assigned to two groups given either colestyramine (n = 13, 7 females/6 males) or HPC (n = 13, 11 females/2 males) (Fernández-Bañares et al., 2015). Both substances were given in the form of 4 g sachets twice daily for 8 weeks. The Panel noted that the two adverse effects (muscle pain, nasopharyngitis) observed in the HPC group seem not to be associated with the intake of HPC, thus HPC is considered to be well tolerated in doses of two or three 4 g sachets per day.

Hydroxypropyl methyl cellulose (HPMC; E 464)

In a study with 25 young and healthy adults (23 males and two females), each person was given three graduated doses of HPMC ranging from 0.6 to 8.9 g. The time interval between the doses was at least 1 week. Following each dose, stool specimens were collected at approximately 24-h intervals for 72 or 96 h. A mild laxative effect was noted in 11 cases and a mild constipating effect in 16 cases (Knight et al., 1952).

Ethyl methyl cellulose (EMC; E 465)

No data available.

Sodium carboxy methyl cellulose (CMC; E 466)

The daily dosing of five male volunteers (age: 24–58 years; body weights: 73–84 kg) with 3 × 5 g of sodium CMC over 23 days was well tolerated. Also routinely examined parameters such as clinical chemistry, haematology, urine analysis, glucose tolerance, serum cholesterol, triglyceride and phospholipids, and breath hydrogen and methane concentrations were not adversely affected. Other effects such as shortening of intestinal transit times, increased faecal weights or changes in faecal bile acids or faecal fat were attributed to an increased cellulose intake without any toxicological significance (Anderson et al., 1986).

In 11 male and female patients with an age of 27–82 years, daily doses of 10 g of sodium carboxy methyl cellulose over 6 months were well tolerated. A haematological examination (RBC and WBC counts, differential smears of WBCs and haematocrit) showed no significant variations. No patients experienced anaemia or a leukopenia and bone marrow studies of three patients during the early part of the test period, as compared to similar studies at the end of 6 months, revealed no changes (Brick, 1952).

In a study with 12 men with an age of 26–62 years and body weights ranging from 77.5 to 111.5 kg, one basal diet containing relatively low-fibre foods was given to the subjects throughout the 20 weeks of the study (Behall et al., 1984). Four fibre sources, locust bean gum, karaya gum, CMC and cellulose were used as the fibre supplements. The four fibre sources were added singly to the basal diet for 4 weeks at the level of 0.75 g fibre/100 cal. The basal di et al one and with the four fibre sources was given in a randomised rotation pattern during the five 4-week dietary periods so that each diet was followed by each of the other diets an equal number of times. The basal diet provided approximately 50.4% of the calories from carbohydrates, 35% from fat and 14.6% from protein. The diet had a P/S ratio of 0.39, and contained 640 mg cholesterol, 27 g crude fibre, and 6.33 g neutral detergent fibre per 2,550 kcal. Caloric intake of the men ranged from 2,550 to 3,600 kcal/day and 19.1 to 27.0 g/day added fibre source, respectively, when given. At the end of each 4-week dietary period, two fasting blood samples were drawn, one for serum analysis and one in ethylenediaminetetraacetic acid (EDTA) to be used for analysis of plasma lipoprotein cholesterol for high-density lipoprotein (HDL), low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL). Fasting serum samples were analysed for cholesterol, triglycerides and free fatty acids (FFA). At the end of the 4 weeks, total serum cholesterol had dropped significantly (from 196 to 164 mg/dL) and

plasma LDL decreased significantly (from 131 to 107 mg/dL). No statistically significant changes were noted for triglycerides, FFA, VLDL, or HDL levels. The ratio of HDL/VLDL+LDL cholesterol was significantly higher than the ratios after consumption of the basal di et al one (0.33 versus 0.28).

Cross-linked sodium carboxy methyl cellulose (E 468)

No data available.

Enzymatically hydrolysed carboxy methyl cellulose (E 469)

No data available.

Summary

Overall, there is no evidence that microcrystalline cellulose or other unmodified celluloses in repeated doses up to 35 g/person adversely affect clinical chemistry and haematological parameters, as well as the absorption and/or the metabolism of dietary constituents.

Several celluloses have been used in patients suffering from diarrhoea or constipation. In general, it can be concluded that an oral uptake of up to 5,000 mg/person per day is well tolerated. Even a daily uptake of 6,000 mg over 4–240 days was well tolerated.

4.2.7.2. Case reports

Cases of oesophageal and GI obstruction have been reported in the literature following intake of methyl cellulose (Belmont, 1952; Hedayaty and Shuman, 1953; Friedman and Alessi, 1954; FDA, 2015), carboxy methyl cellulose (Leger et al., 1952; Monod-Broca, 1952; Soullard et al., 1952; Derobert and Heully, 1956; FDA, 2015) and cellulose fibre diet pills (Jones and Pillsbury, 1990).

5. Discussion

The present opinion deals with the re-evaluation of the safety of microcrystalline cellulose (E 460(i)), powdered cellulose (E 460(ii)), methyl cellulose (E 461), ethyl cellulose (E 462), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464), ethyl methyl cellulose (E 465), sodium carboxy methyl cellulose (E 466), cross-linked sodium carboxy methyl cellulose (E 468) and enzymatically hydrolysed carboxy methyl cellulose (E 469) as food additives. These celluloses are authorised as food additives in accordance with Annex II and Annex III of Regulation (EC) No 1333/2008.

Cellulose is a linear glucose homopolymer consisting of glucopyranose units linked by β-1,4-glycosidic bonds; its molecular formula is $(C_6H_{10}O_5)_m$, with the DP dependent on the origin of the cellulolytic material. Cellulose molecular weight has been calculated to fall approximately in the range 50,000–2,500,000. In modified celluloses, the chemical and physical characteristics of the native substances are modified in order to confer different technological properties for particular food applications. They are obtained from fibrous plant material and the modifications consist mainly in depolymerisation, etherification (with methyl, ethyl or hydroxypropyl groups), or the formation of salt of the carboxymethyl ether of native cellulose. The preparation of modified celluloses can also involve physical (E 460(ii)) or enzymatic treatments (E 469).

Animal and human data clearly demonstrated that microcrystalline cellulose (E 460(i)) and powdered cellulose (E 460(ii)) are not absorbed intact in the GI tract but could be fermented during their passage through the large intestine by strains of bacteria found in the human colon, although to a lesser degree than other polysaccharides such as gums, starches or pectins. Data for methyl cellulose (E 461), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464), ethyl methyl cellulose (E 465), sodium carboxy methyl cellulose (E 466), cross-linked sodium carboxy methyl cellulose (E 468) and enzymatically hydrolysed carboxy methyl cellulose (E 469) demonstrated that these modified celluloses are not absorbed intact, not fermented and are excreted intact via the faeces.

Data on acute oral toxicity are available for microcrystalline cellulose (E 460(i)), powdered cellulose (E 460(ii)), ethyl cellulose (E 462), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464) and sodium carboxy methyl cellulose (E 466). These data indicate low oral acute toxicity, which would also apply to the other celluloses for which specific data were not available.

Short-term and subchronic toxicity studies have been performed with microcrystalline cellulose (E 460(i)), powdered cellulose (E 460(ii)), methyl cellulose (E 461), ethyl cellulose (E 462), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464), sodium carboxy methyl cellulose (E 466), cross-linked sodium carboxy methyl cellulose (E 468) and enzymatically hydrolysed carboxy methyl cellulose (E 469). In the majority of studies, animals were dosed via diet at levels up to 10%. Effects on body weight at the highest dose tested (10%) were reported in some, but not all

studies, which may reflect nutritional constraints rather than toxicity. No adverse effects were reported with most of the tested celluloses, except for local effects on caecal size due to the presence of undigested fibre. Groups of 20 Wistar rats per sex were dosed with sodium carboxy methyl cellulose (E 466) or enzymatically hydrolysed carboxy methyl cellulose (E 469) via diet with 0%, 2.5%, 5% and 10% (up to 6,800 mg/kg bw per day) for up to 102 days (Til, 1992; Bär et al., 1995a). Effects on caecal weight, urothelial hyperplasia, pelvic nephrocalcinosis, corticomedullary nephrocalcinosis and increased incidence of diffuse epithelial hyperplasia in the urinary bladder were observed. The findings in kidneys and urinary bladder were attributed to the concentration of sodium, which was up to fourfold higher in the test diet compared with the basal diet. The Panel noted that this was a plausible explanation for the reported findings.

Data concerning genotoxicity are available for microcrystalline cellulose (E 460(i)), methyl cellulose (E 461) and sodium carboxy methyl cellulose (E 466) (Litton Bionetics Inc., 1974, 1975, 1980; Blevins and Taylor, 1982; Ishidate et al., 1984; Batt, 1992; Cifone, 1992; McKeon, 1992; FMC, 1991, 1994, 1995; Murli, 1992). Overall, despite the limitations of some of the studies, the Panel concluded that the available data and the *in silico* analysis conducted by the Panel, did not identify structural determinants indicating a genotoxic concern for microcrystalline cellulose, methyl cellulose and carboxy methyl cellulose. The Panel considered that these results could be read-across to the other modified and unmodified celluloses covered by this opinion, for which the same conclusion can be reached.

Chronic toxicity studies have been performed with microcrystalline cellulose (E 460(i)), methyl cellulose (E 461), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464), ethyl methyl cellulose (E 465) and sodium carboxy methyl cellulose (E 466). Although there were some inconsistencies in the data, the main effects seen were decreases in body weight gain at the highest dose, which are likely to be due to the amount/bulk of celluloses in the diet leading to nutritional imbalance. Furthermore, in a chronic feeding study with microcrystalline cellulose (E 460(i)), some dystrophic calcification of renal tubules was observed in the high dose group (15,000 mg/kg bw per day). The NOAEL values ranged up to 9,000 mg/kg bw per day. The Panel concluded that microcrystalline cellulose and modified celluloses have no carcinogenic properties and that there was no reason to expect carcinogenic properties with powdered cellulose (E 460(ii)).

Concerning reproductive and developmental toxicity, data are available for microcrystalline cellulose (E 460(i)), methyl cellulose (E 461), hydroxypropyl cellulose (E 463) and sodium carboxy methyl cellulose (E 466). The substances were tested in mice, rats, hamsters and/or rabbits with oral dosing via gavage (FDLI, 1973, 1975; Ferch, 1973a,b; Cannon Labs, 1975, 1977; Kitagawa et al., 1978a,b; Fritz and Becker, 1981; Freeman, 1992b). Adverse effects on reproductive performance or developmental effects were not observed with modified and unmodified celluloses at doses greater than 1,000 mg/kg bw by gavage (often the highest dose tested).

Specific toxicity data were not always available for all the celluloses for all endpoints. In general, the most complete data sets were available for microcrystalline cellulose (E 460(i)) and sodium carboxy methyl cellulose (E 466). Given the similarities in their structure, relevant physicochemical, metabolic and toxicological properties, the Panel considered it possible to read-across between all the celluloses.

In addition, the Panel noted that methyl cellulose (E 461) and sodium carboxy methyl cellulose (E 466) were frequently used in the formulations for administration of xenobiotics by gavage in chronic, reproductive and developmental toxicity and carcinogenicity studies. In these studies, there should be a control group receiving the formulation alone. Although modified cellulose levels were usually only up to 2%, given the number of studies and group sizes in these studies, the overall number of animals tested would be very large. The Panel considered that the absence of reported adverse effects from such vehicle control groups provided additional evidence of the lack of safety concern for modified celluloses at levels up to 2% in the vehicle.

There was evidence that repeated doses up to 35 g/person of microcrystalline cellulose or powdered cellulose did not adversely affect clinical chemistry and haematological parameters and had no effect on the absorption and/or the metabolism of dietary constituents.

Some modified celluloses have been used in patients suffering from diarrhoea or constipation. In general, it can be concluded that an oral ingestion of up to 6,000 mg/person per day for 8 months was well tolerated.

Carboxy methyl cellulose was one of the food additives reported to alter the gut microbiota, promote gut inflammation, promote obesity and to impair glycaemic control in mice (Chassaing et al., 2015). Other emulsifiers have been reported to alter the gut microbiota, promote gut inflammation, promote obesity and to impair glycaemic control in experimental studies with animals (Swidsinski

et al., 2009a,b; Renz et al., 2012; Merga et al., 2014; Cani and Everard, 2015; Chassaing et al., 2015; Romano-Keeler and Weitkamp, 2015; Lecomte et al., 2016; Shah et al., 2017).

The Panel noted that some of the effects associated with emulsifiers are not systematically studied as specific endpoints in toxicity studies performed according to current toxicity testing guidelines, therefore, they would have be investigated on a case-by-case basis if indicated by the results of the general toxicity testing, as recommended in the Guidance for submission of food additives (EFSA ANS Panel, 2012). However, the Panel noted that the histopathological findings reported in some of the studies are not seen in long-term studies at high doses of celluloses.

The Panel considered that based on the animal data, the toxicity of microcrystalline, powdered and modified celluloses was low and that NOAELs were generally the highest dose tested (up to at least 9,000 mg/kg bw per day). The available data in humans indicate that daily doses of up to 6,000 mg for around 8 months were not associated with adverse effects; however in line with many other dietary fibres, large bolus intakes of celluloses were occasionally associated with laxation, but there was a lack of dose–response data available. Overall, there were no indications that humans would be more sensitive than laboratory animals.

The Panel considered that in line with the conceptual framework, it would be useful if risk managers had an indicative total exposure (daily consumption value) for microcrystalline, powdered and modified celluloses used as food additives, which would not pose a safety concern and uses up to this value would not require a further risk assessment. The Panel considered this could be based on all the reported NOAELs from subchronic and chronic toxicity studies (ranging from 2100 to more than 9000 mg/kg bw/day either the highest doses tested or the highest doses tested not inducing nutritional imbalance)taking into account human data and allowing for interindividual uncertainty. The Panel considered that an indicative total exposure (daily consumption value) of around 660 to 900 mg/kg bw per day for microcrystalline, powdered and modified celluloses could be identified.

To assess the dietary exposure to celluloses (E 460–466, E 468 and E 469) from their use as food additives, the combined exposure was calculated based on (1) maximum levels of data provided to EFSA (defined as the *maximum level exposure assessment scenario*) and (2) reported use levels (defined as the *refined exposure assessment scenario brand-loyal* and *non-brand-loyal consumer scenario*).

Celluloses (E 460–466, E 468 and E 469) are authorised in a wide range of foods. The Panel did identify brand loyalty to specific food categories in infants and toddlers (e.g. flavoured drinks). Further, the Panel considered that the non-brand-loyal scenario covering other population groups was appropriate and a realistic scenario for risk characterisation because it was assumed that the population would probably be exposed long-term to the food additive present at the mean reported use level in processed food.

A refined estimated exposure assessment scenario taking into account the FSMP for infants and young children (FC 13.1.5.1 dietary foods for infants for special medical purposes and special formulae for infants and 13.1.5.2 dietary foods for babies and young children for special medical purposes as defined by Commission Directive 1999/22/EC in which E 466 is authorised) was also performed to estimate exposure for infants and toddlers who may be on a specific diet. However, no reported use levels were made available by industry for these food categories. Thus, MPLs of E 466 for FSMP were used. The Panel noted that according to Mintel, very few baby foods were on the European market containing E 466. This was in line with the fact that no data were submitted for the food categories 13.1.5.1 and 13.1.5.2.

A refined estimated exposure assessment scenario taking into account the consumption of food supplements for consumers only was also performed to estimate exposure for children, adolescents, adults and the elderly, as exposure via food supplements may deviate largely from that via food, and the number of food supplements consumers may be low depending on populations and surveys.

The refined estimates were based on 26 out of 84 food categories in which celluloses (E 460–466, E 468 and E 469) are authorised. The Panel considered that the uncertainties identified would, in general, result in an overestimation of the exposure to celluloses (E 460–466, E 468 and E 469) as food additives in European countries considered in the EFSA European database for the refined scenario if it is considered that the food additives may not be used in food categories for which no usage data have been provided.

The Panel noted that given the information from the Mintel's GNPD, it may be assumed that celluloses (E 460–466, E 468 and E 469) are used in food categories for which no data have been provided by food industry. The main food categories, in terms of amount consumed, not taken into account were processed fermented milk products, cheeses (unripened, processed), fish and fishery

products and breakfast cereals. However, according to the Mintel GNPD (Appendix B), in the EU market, a small percentage (< 1%) of food products belonging to these food categories are labelled with celluloses (E 460–466, E 468 and E 469). Therefore, the Panel considered that if these uncertainties were confirmed, it would result in a slight underestimation of the exposure.

The Panel further noted that the exposure to celluloses (E 460–466, E 468–469) from their use according the Annex III to Regulation (EC) No 1333/2008 was not considered in the exposure assessment.

The Panel also noted that the refined exposure estimates were based on information provided on the reported levels of use of celluloses (E 460–466, E 468–469). If actual practice changes, this refined estimates may no longer be representative and should be updated.

6. Conclusions

General population

Following the conceptual framework for the risk assessment of certain food additives re-evaluated under Commission Regulation (EU) No 257/2010 (EFSA ANS Panel, 2014) and given that:

- their structural, physicochemical and biological similarities, allows for read-across between all the celluloses
- animal and human data demonstrate that microcrystalline cellulose (E 460(i)) and powdered cellulose (E 460(ii)) are not absorbed intact in the GI tract but could be fermented by intestinal microbiota. Chemically modified celluloses are not absorbed intact, nor fermented, but are excreted intact via the faeces
- using the read-across approach, adequate data on short- and long-term toxicity and carcinogenicity and reproductive toxicity are available,
- despite the limitations of some of the studies, the available data do not indicate a genotoxic concern for microcrystalline cellulose, methyl cellulose and carboxy methyl cellulose, and by read-across, of the other modified and unmodified celluloses
- no adverse effects were reported after repeated doses up to 35 g/person of microcrystalline cellulose or powdered cellulose; oral ingestion of some modified celluloses up to 6,000 mg/person per day for 8 months in patients suffering from diarrhoea or constipation was well tolerated;
- adequate combined exposure data were available; in the general population, the highest 95th percentile refined exposure assessment estimates calculated based on the reported data from food industry was 506 mg/kg bw per day in toddlers (brand-loyal scenario)
- an indicative high refined exposure assessment of up to 448 mg/kg bw per day for the elderly has been calculated at the 95th percentile among the population classes consuming food supplements

The Panel concluded that there was no need for a numerical ADI and that there would be no safety concern at the reported uses and use levels for the unmodified and modified celluloses (E 460(i); E 460(ii); E 461–466; E 468 and E 469). The Panel further suggested an indicative total exposure (daily consumption value from food additive use) of 660–900 mg/kg bw per day where these conclusions would remain valid.

Infants and young children consuming foods for special medical purposes and special formulae

Concerning the use of sodium carboxy methyl cellulose (E 466) in 'dietary foods for special medical purposes and special formulae for infants' (FC 13.1.5.1) and in 'dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC' (FC 13.1.5.2), and given that:

- for infants and toddlers consumers only of FSMP, the highest 95th percentile refined exposure estimate was 1,557 mg/kg bw per day in infants
- no adequate specific studies addressing the safety of use of sodium carboxy methyl cellulose (E 466) in this population under certain medical conditions were available;

the Panel concluded, that the available data did not allow for an adequate assessment of the safety of use of sodium carboxy methyl cellulose (E 466) in infants and young children consuming foods belonging to the categories 13.1.5.1 and 13.1.5.2. The Panel noted that E 466 seemed not to be used in these food categories as no use or use levels were submitted by industry and only very few food belonging to these categories appeared to be labelled with E 466.

7. Recommendations

The Panel recommended that:

- The European Commission considers lowering the maximum limits for the toxic elements arsenic, lead, mercury and cadmium present as impurities in the EU specifications for unmodified and modified celluloses re-evaluated in the present opinion (E 460(i), E 460(ii), E 461, E 462, E 463, E 464, E 465, E 466, E 468, E 469) should be revised to ensure that these food additives will not be a significant source of exposure to these toxic elements in food.

Documentation provided to EFSA

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Abbreviations

AAS	atomic absorption spectroscopy
ADI	acceptable daily intake
AESGP	Association of the European Self-Medication Industry
AGU	anhydroglucose unit
AHP-WS	wheat straw pretreated with alkaline hydrogen peroxide
ANS Panel	EFSA Panel on Food Additives and Nutrient Sources added to Food
AOAC	Association of Official Analytical Chemists
AP	alkaline phosphatase
BUN	blood urea nitrogen
bw	body weight
CAS	Chemical Abstract Service
CHL	Chinese hamster fibroblast cell line
CHO	Chinese hamster ovary cells
CMC	carboxy methyl cellulose

DMSO	dimethylsulfoxide
DP	degree of polymerisation
DS	degree of substitution (the average number of substituted hydroxyl groups per glucose)
EDA	European Dairy Association
EDTA	ethylenediaminetetraacetic acid
EHPM	European Federation of Associations of Health Products Manufacturers
EINECS	European Inventory of Existing Commercial Chemical Substances
EMA	European Medicines Agency
EMC	ethyl methyl cellulose
FAO	Food and Agriculture Organization
FC	freezing–cooking
FCS	Food Classification System
FDA	Food and Drug Administration
FDE	FoodDrinkEurope
FFA	free fatty acids
FSE	Food Supplements Europe
FSMP	food for special medical purpose
GALT	gut-associated lymphoid tissue
GC	gas chromatography
GD	gestation day
GI	gastrointestinal
GLP	good laboratory practice
GNPD	Global New Products Database
GPC	gel permeation chromatography
GRAS	Generally Recognized as Safe
Hb	haemoglobin
HDL	high-density lipoprotein
HMWSDF	high-molecular weight soluble dietary fibres
HPC	hydroxypropyl cellulose
HPLC	high-performance liquid chromatography
HPMC	hydroxypropyl methyl cellulose
ICGA	International Chewing Gum Association
ICP-AES	inductively coupled plasma atomic emission spectroscopy
IR	infrared
JECFA	Joint FAO/WHO Expert Committee on Food Additives
L-HPC	hydroxypropyl cellulose of low substitution
LD_{50}	lethal Dose, 50% i.e. dose that causes death among 50% of treated animals
LDL	low-density lipoprotein
MA	metabolic activation
MALDI MS	matrix-assisted laser desorption/ionisation mass spectrometry
MC	methyl cellulose
MCC	microcrystalline cellulose
MHEC	methyl hydroxyethyl cellulose
MPL	maximum permitted level
MS	mass spectrometry
NaCMC	sodium carboxy methyl cellulose
NDA Panel	EFSA Panel on Dietetic Products, Nutrition and Allergies
NDO	non-digestible oligosaccharides
NMR	nuclear magnetic resonance
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
OFCA	Organisation des Fabricants de produits Cellulosiques Alimentaires
OM	organic matter
OPEFB	oil palm empty fruit pulp
PCV	packed cell volume
PCH	propylene chlorohydrin
PMC	propyl methyl cellulose

QS	*quantum satis*
RBC	red blood cell
SCF	Scientific Committee on Food
SCFA	short-chain fatty acids
S-GOT	serum glutamic-oxaloacetic transaminase
S-GPT	serum glutamate pyruvate transaminase
TAMC	total anaerobic microbial count
TYMC	total combined yeast and mould count
UV/VIS	ultraviolet/visual (spectrometry)
VFA	volatile fatty acids
VLDL	very low-density lipoprotein
WBC	white blood cell
WG	Working Group
WHO	World Health Organization

Appendix A – Summary of the reported use levels (mg/kg or mg/L as appropriate) of celluloses (E 460–466, E 468 and E 469) provided by industry

Appendix B – Number and percentage of food products labelled with celluloses (E 460–466, E 468 and E 469) out of the total number of food products present in the Mintel GNPD per food subcategory between 2012 and 2017

Appendix C – Concentration levels of celluloses (E 460–466, E 468 and E 469) used in the refined exposure scenarios (mg/kg or mL/kg as appropriate)

Appendix D – Total estimated exposure of celluloses (E 460–466, E 468 and E 469) from its use as a food additive for the maximum level exposure scenario and the refined exposure assessment scenarios per population group and survey: mean and 95th percentile (mg/kg bw per day)

Appendix E – Main food categories contributing to exposure to celluloses (E 460–466, E 468 and E469) for the maximum and refined (brand-loyal and non-brand-loyal) scenarios

Appendix A–E can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2018.5047

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization or of the Food and Agriculture Organization of the United Nations

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JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES

Rome, 29 May–7 June 1989

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Monographs containing summaries of relevant data and toxicological evaluations are available from WHO under the title:

Toxicological evaluation of certain food additives and contaminants. WHO Food Additives Series, No. 26, in press.

Specifications are issued separately by FAO under the title:

Specifications for the identity and purity of certain food additives. (To be published as an FAO Food and Nutrition Paper.)

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

The preparatory work for toxicological evaluations of food additives and contaminants by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) is actively supported by certain of the Member States that contribute to the work of the International Programme on Chemical Safety (IPCS).

The International Programme on Chemical Safety (IPCS) is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. One of the main objectives of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment.

EVALUATION OF CERTAIN FOOD ADDITIVES AND CONTAMINANTS

Thirty-fifth Report of the Joint FAO/WHO Expert Committee on Food Additives

The Joint FAO/WHO Expert Committee on Food Additives met in Rome from 29 May to 7 June 1989. The meeting was opened by Dr P. Lunven, Director, Food Policy and Nutrition Division, FAO, on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations and the World Health Organization. Dr Lunven noted that the work of the Joint FAO/WHO Committee on Food Additives in providing scientific assessments was invaluable to WHO, FAO, and Member States and, in particular, to the work of the Codex Alimentarius Commission. The Commission had been recognized as one of the key elements in removing barriers to trade and was expanding its work on food additives to provide uniform and comprehensive recommendations to governments. Dr Lunven also noted that a comprehensive compilation of specifications for the identity and purity of food additives was in preparation for publication.[1]

1. INTRODUCTION

As a result of the recommendations of the first Joint FAO/WHO Conference on Food Additives, held in September 1955 (*1*), there have been 34 previous meetings of the Expert Committee (Annex 1). The present meeting was convened on the recommendation made at the thirty-third meeting (Annex 1, reference *83*).

The tasks before the Committee were: (*a*) to prepare specifications for the identity and purity of certain food additives and to carry out toxicological evaluations of them; (*b*) to review specifications for selected food additives; and (*c*) to undertake toxicological evaluations of certain food additives and the contaminants polychlorinated biphenyls and patulin.

[1] *Specifications for the identity and purity of food additives* (being prepared by FAO).

2. GENERAL CONSIDERATIONS

2.1 Modification of the agenda

The issue of the safety of certain fungal enzyme preparations used in food was added to the agenda.

Four flavouring agents, dihydrocoumarin, ethyl vanillin, fumaric acid, and quinine hydrochloride, were placed on the agenda on the basis of application of the first three steps of the method for setting priorities for the safety review of food flavouring ingredients, which is summarized in the report of the thirty-third meeting (Annex 1, reference *83*).

2.2 Principles governing the toxicological evaluation of compounds on the agenda

In making recommendations on the safety of food additives and contaminants, the Committee took into consideration the principles established and contained in *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*). This publication, developed in response to repeated recommendations by the Committee, embraces the major observations, comments, and recommendations on the safety assessment of food additives and contaminants contained in the previous reports of the Committee and other associated bodies. The Committee noted that the document reaffirms the validity of recommendations that are still appropriate, and points out the problems associated with those that are no longer valid in the light of modern technical advances.

2.2.1 *Enzyme preparations*

In conjunction with the revision of general specifications for enzyme preparations (section 4.2), the Committee briefly reviewed the guidelines for evaluating enzyme preparations used in food processing that are given in Annex 3 of *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*).

It concluded that these guidelines provide a logical hierarchical procedure for determining the amount and kind of data required to establish the safety in use of enzyme preparations. The Committee stressed the advisory nature of the guidelines and recommended that

they and others given in Annex 3 of *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*) be reviewed at a future meeting.

2.2.2 *Flavouring agents*

Flavouring agents have been the subject of general comments in several previous reports of the Committee and in *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*). The view has repeatedly been expressed that, although flavouring agents should ideally be toxicologically evaluated in the same way as other food additives, special considerations dictate a degree of flexibility.

Although minimum requirements for the safety evaluation of flavouring agents have not been specified, any such evaluation should, in general, include at least a short-term feeding study, relevant metabolism studies, and mutagenicity studies.

The Committee had before it a number of flavouring agents for evaluation. In many instances, however, as is evident from section 3.1.3, the Committee had difficulty in carrying out an evaluation since data were lacking.

The Committee recognized the special problems involved in the safety evaluation of flavouring agents. However, it emphasized that a minimum amount of data was necessary to permit the development of a flexible procedure for evaluating these substances.

2.2.3 *Group ADIs for compounds that have a laxative effect*

In allocating a group acceptable daily intake (ADI) "not specified" to modified celluloses (section 3.1.5) and drawing attention to the laxative effect of an excessive intake of these substances, the Committee noted that similar considerations applied to polyols and that some gums and modified starches might also cause laxative effects at high intakes. At the Committee's twenty-seventh meeting (Annex 1, reference *62*), it was recommended that controls should be introduced to limit the consumption of polyols from all sources. At its present meeting, the Committee considered that other groups of thickeners and stabilizers that have laxative effects should also be subject to these controls since their effects are likely to be additive.

2.3 Principles governing the establishment and revision of specifications

2.3.1 *General*

The Committee reaffirmed the importance of specifications for identity and purity in the evaluation and safe use of food additives, as set out in *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*). Material subjected to toxicological testing should always be adequately defined. The Committee stressed that information on methods of manufacture, raw materials, and potential impurities should be assessed on a regular basis so that specifications can be drawn up that are both appropriate to the material used in food and consistent with the composition of the material toxicologically tested or evaluated.

In updating existing specifications, the Committee recognized the need, in certain instances, to change the terms "molecular weight" and "relative molecular mass" to "formula weight" in order to conform to accepted chemical principles (*2*). The Committee considered the term formula weight, which represents the mass corresponding to the simplest or empirical formula of a chemical compound, to be the correct term both for salts and for other chemicals that do not exist in nature as discrete molecules. Specifications reviewed at the present meeting were revised, where necessary, in accordance with this principle.

2.3.2 *Enzyme preparations*

Enzyme preparations were considered at the present meeting in response to a recommendation made at the Committee's thirty-first meeting. Questions had arisen from a discussion of the need to define the non-enzymic components of enzyme preparations and how information on such components might be taken into account from the point of view of the definition and safety of the products. The Committee concluded that a complete definition of all the components of an enzyme preparation can rarely, if ever, be achieved and that the identity and purity of preparations can therefore best be ensured by defining the processes by which they are produced and establishing criteria limiting the presence of contaminants and possible toxic metabolites derived from the source material or contaminating organisms.

The uncertainty as to the nature of the non-enzymic components mainly concerns the components that are derived in association with the active enzyme from the source material. In the case of enzymes derived from microbial sources, the potential for variability is related to both the identity of the organism concerned and the conditions under which it is cultured during the production of the enzyme. The Committee considered that it would be desirable, in specifications for microbial enzyme preparations, to define the source organism in terms not only of the species concerned but also of the strain or variant and to ensure that the culture conditions employed during the production of any particular preparation were the same as those under which the preparation subjected to toxicological testing was produced. Differences in either the strain of source organism or the conditions under which it was cultured would imply a change in the identity of the preparation and therefore require its re-evaluation. The Committee reiterated the principle already incorporated in the existing general specifications for enzyme preparations used in food processing (Annex 1, reference *69*) that non-enzymic components added for technological reasons (stabilizers, diluents, preservatives, etc.) and as immobilizing agents should be acceptable and appropriate for the intended uses of the enzyme preparations in food and food processing.

The Committee recognized that it may be inappropriate to impose limits on named mycotoxins in all microbial enzyme preparations regardless of source organism. It considered that, as individual specifications for enzymes are reviewed, the limits on named mycotoxins in the general specifications should be transferred, where relevant, to the individual source organisms. The Committee remained concerned, however, about the possibility of the production of as yet unidentified toxic metabolites. It considered that an appropriate battery of tests to screen for such potentially toxic metabolites should be developed for inclusion in the general specifications for enzyme preparations from microbial sources.

2.3.3 *Naturally occurring substances*

Substances of natural origin (e.g., spice oleoresins) may be introduced into commerce in forms that vary widely in composition. This variation is attributable to a number of factors, including the existence of different cultivars, the effects of climate and geography, the use of different extraction solvents and procedures, and the use

of diluents. Because of such compositional variation, specifications have tended to be broad and therefore not necessarily relevant to the substance for which a toxicological evaluation may be available. The Committee believed that specifications that simply state, for example, the content of the principal component (e.g., flavouring principle, colour principle) as "not less than declared on the label", while suitable for ensuring honesty in trade, could be inadequate for purposes of safety. It therefore recognized the need to continue exploring new principles for establishing adequate specifications for substances of natural origin that are both appropriate to the material used in food and consistent with the composition of the toxicologically evaluated material.

2.3.4 *Solvent residues*

During its deliberations on specifications for spice oleoresins, the Committee expressed the opinion that the use of dichloromethane and 1,2-dichloroethane as extraction solvents should be discouraged because of toxicological concerns. Because these and other solvents have not been recently evaluated and new data are now available, the Committee concluded that an overall review of solvents used in food processing would be appropriate.

In future reviews of existing specifications where provision has been made for the use of solvents, the Committee intends to request the user industry to provide justification for their use in addition to more specific data on typical levels of residues resulting from such use.

The Committee further stressed that levels of residues resulting from the use of any solvent should be the minimum technically achievable and toxicologically insignificant. Research leading to the development of new solvent systems of lower toxic potential is to be encouraged.

2.4 Methodology for analysing chemical contaminants in food

For assessing the health implications of dietary exposure to chemical contaminants, reliable information on the intake of such substances is needed. In particular, data are required on the actual levels of the substances of interest in various foods, and it is necessary to ensure that the analytical procedures employed to generate these data are both reliable and of adequate accuracy.

In connection with the chemical contaminants evaluated at its present meeting, the Committee was aware of the difficulties that could be encountered in the analysis of polychlorinated biphenyls (PCBs) in food and, in particular, in PCB isomer-specific analysis. It was informed of the ongoing activities of the WHO Regional Office for Europe related to PCBs (as well as other chlorinated hydrocarbons, including polychlorinated dibenzodioxins and polychlorinated dibenzofurans) and the assessment of health risks to infants associated with contamination of mothers' milk. Part of this project involves interlaboratory quality-control studies on levels of PCBs in human milk, and the results of the first round of such studies, which involved 12 laboratories, have been published (*3*). Planning of the second round of quality-control studies has already begun, and additional laboratories are expected to participate. The Committee expressed its support for studies of this type.

In the case of patulin, the results of numerous surveys of fruit products have been published over the last two decades. However, in many of the older surveys, the methods used were not sufficiently sensitive, and patulin was not positively identified. The Committee's evaluation of this mycotoxin took account of these facts.

3. COMMENTS ON SPECIFIC FOOD ADDITIVES AND CONTAMINANTS[1]

The Committee evaluated a number of food additives and contaminants for the first time and re-evaluated several substances considered at previous meetings. Information on the evaluations and on specifications is summarized in Annex 2. Details of further toxicological studies and of other information required or desired for certain substances are given in Annex 3.

3.1 Specific food additives

3.1.1 *Emulsifiers*

Polyglycerol esters of fatty acids

At the Committee's seventeenth meeting (see Annex 1, reference *32*), polyglycerol esters of fatty acids were evaluated and the

[1] Bibliographical references to toxicological studies are included in this section only for substances for which toxicological monographs (which would normally list such references) have not been prepared.

Committee agreed to convert the former conditional ADI to an ADI of 0–25 mg per kg of body weight.

At its thirty-first meeting (see Annex 1, reference *77*), the Committee revised the specifications but was unable to accept the request to increase the range of average polyglycerol chain lengths permitted from three to ten glycerol units without a review of the toxicological data on these substances. Since the data requested were not forthcoming, the Committee at its present meeting maintained the previous ADI of 0–25 mg per kg of body weight for polyglycerol esters of fatty acids having an average chain length of up to three glycerol units.

A toxicological monograph was not prepared.

The existing specifications for polyglycerol esters of fatty acids were maintained.

Sucrose esters of fatty acids and sucroglycerides

Sucrose esters of fatty acids are the mono-, di-, and triesters of sucrose with edible fatty acids. They may be prepared from sucrose and the methyl and ethyl esters of edible fatty acids, usually in the presence of a solvent. "Sucroglycerides" (a mixture of sucrose esters of fatty acids and mono- and diglycerides) are produced by reaction of edible fats or oils with sucrose; this reaction is also usually carried out in the presence of a solvent.

These substances were evaluated for the purpose of establishing an ADI at the Committee's thirteenth, seventeenth, twentieth, and twenty-fourth meetings (Annex 1, references *19, 32, 41,* and *53*). Separate toxicological monographs were prepared on each occasion for sucrose monoesters of individual fatty acids and for palm-oil sucrose esters and lard and tallow sucrose esters.

At its present meeting, the Committee was asked to consider the consequences of modifying the specifications for these substances when manufactured by a process in which dimethylsulfoxide, isobutanol, ethyl methyl ketone, or a combination of these is used as solvent. It was noted that an ADI (or provisional intake) had not been established for these solvents but that dimethylsulfoxide and isobutanol occur naturally in the diet and ethyl methyl ketone has been identified as a product of intermediary metabolism. The Committee concluded that, in foods as consumed, the levels of these solvents arising from residues in sucrose esters of fatty acids that comply with the specifications (as revised at the present meeting) are

insignificant relative to naturally occurring levels in the diet, and there is no reason to suppose that they present a hazard.

The Committee also reviewed new toxicological studies on a palm-oil sucroglyceride, including a long-term carcinogenicity study in rats and short-term studies in rats and dogs.

It was concluded that, both for sucrose esters of fatty acids manufactured by a process using dimethylsulfoxide, isobutanol, ethyl methyl ketone, or a combination of these as solvent, and for the palm-oil sucroglyceride, the previously established group ADI of 0–10 mg per kg of body weight for sucrose esters of fatty acids and sucroglycerides would apply.

An addendum to the toxicological monograph was prepared.

The specifications for sucrose esters of fatty acids were revised to include considerations on the use of the above-mentioned solvents.

The existing specifications for sucroglycerides were maintained.

3.1.2 *Enzyme preparations*

Enzyme preparations derived from Aspergillus niger

As a consequence of its review of general specifications for enzyme preparations, the Committee reconsidered the evaluation of enzymes derived from *Aspergillus niger* made at the thirty-first meeting (Annex 1, reference 77). At that meeting, the Committee established a single ADI for several separate enzyme preparations derived from *Aspergillus niger* of 0–1 mg of total organic solids per kg of body weight. The enzyme preparations for which this ADI was established were carbohydrases, amyloglucosidases (EC 3.2.1.3), endo-1,3(4)-β-glucanase (EC 3.2.1.6), hemi-cellulase, pectinases (EC 3.1.1.11; 4.2.2.10; 3.2.1.15), and protease.

In view of the fact that *Aspergillus niger* is a common organism in food, that many strains have had a long history of use as an enzyme source, and that the numerous studies of various preparations from various strains have demonstrated no hazard to human health, the numerical ADI that was earlier established for each of the above-listed enzyme preparations from *Aspergillus niger* was changed to an ADI "not specified".

A toxicological monograph was not prepared.

None of the existing specifications for enzyme preparations derived from *Aspergillus niger* were reviewed.

3.1.3 *Flavouring agents*

Benzyl acetate

This compound was previously reviewed at the eleventh, twenty-seventh, twenty-ninth, and thirty-first meetings of the Committee (Annex 1, references *14, 62, 70,* and *77*).

At the thirty-first meeting, the Committee extended the temporary ADI of 0–5 mg per kg of body weight pending the evaluation of lifetime gavage studies with benzyl alcohol, a normal metabolite of benzyl acetate. These studies did not show an increased incidence of either hepatocellular or forestomach tumours in mice or pancreatic tumours in rats, although such effects had previously been observed in studies with benzyl acetate. However, there are difficulties in interpreting the results of the carcinogenicity studies with benzyl acetate since the compound was given by gavage. Since new long-term studies are under way with benzyl acetate incorporated into the diet of rats and mice, the Committee decided to extend the temporary ADI of 0–5 mg per kg of body weight until 1993 pending the evaluation of the results of these studies.

In view of a report of a positive result in an *in vitro* mutagenicity test on benzyl acetate, the Committee concluded that it would be desirable to ascertain whether the results of an existing *in vivo* study that demonstrated the absence of the induction of unscheduled DNA synthesis could be confirmed by an *in vivo* test for chromosome damage in bone marrow.

A toxicological monograph was prepared.

The existing specifications for benzyl acetate were maintained.

Cinnamaldehyde

Cinnamaldehyde was evaluated at the eleventh, twenty-third, twenty-fifth, and twenty-eighth meetings of the Committee (Annex 1, references *14, 50, 56,* and *66*).

At its twenty-third meeting, the Committee converted the previously established conditional ADI of 0–1.25 mg per kg of body weight into a temporary ADI of 0–0.07 mg per kg of body weight (Annex 1, reference *50*) because of inadequacies in the toxicity data. At the twenty-eighth meeting, the temporary ADI was extended and an extensive series of studies was requested.

Because the required data were not forthcoming, the Committee was unable to extend the temporary ADI at its present meeting. However, the Committee concluded that, of the information

requested at the twenty-eighth meeting, the results of the short-term feeding study in a non-rodent mammalian species and of adequate metabolic studies might be sufficient to make re-evaluation possible.

A toxicological monograph was not prepared.

The existing specifications for cinnamaldehyde were maintained.

Dihydrocoumarin

The safety of this substance was evaluated for the first time by the Committee at its present meeting.

Metabolites of dihydrocoumarin identified in rabbit urine include umbelliferone, 3-hydroxycoumarin, coumarin, *o*-coumaric acid, melilotic acid, melilotoylglycine, and *o*-coumaroylglycine (*4*). There is some evidence that the gut flora is responsible for the conversion to melilotic acid (*5*).

The toxicological information available was derived from acute toxicity tests in mice (*6*), rats (*7, 8*), and guinea-pigs (*7*), a 14-week study in rats in which loss of test compound in the diet mixture during storage precluded estimation of exact exposure levels (*9*), a short-term study in rats (90 days), in which a single dose level was used (*10*), and a study in which three dogs were treated at one of two dose levels of dihydrocoumarin for two years but for which there was no control group (*9*). Although no adverse effects were reported in these studies, the Committee considered the data inadequate for toxicological evaluation and was therefore unable to allocate an ADI for dihydrocoumarin. The Committee stated that, for a re-evaluation of this substance, the results of a short-term study in a rodent species and metabolic studies to investigate the extent of conversion to coumarin would be needed.

A toxicological monograph was not prepared.

New specifications were prepared for dihydrocoumarin and were designated as tentative. Further information is required (see Annex 3).

Ethyl vanillin

Ethyl vanillin was previously evaluated at the eleventh meeting of the Committee (Annex 1, reference *14*), when an ADI of 0–10 mg per kg of body weight was allocated to this compound on the basis of a long-term study in rats. Although the Committee had then considered it possible to allocate an ADI, it had noted that few metabolic studies were available and concluded that further studies of that type were desirable.

Ethyl vanillin was placed on the agenda of the present meeting on the basis of partial application of the method for setting priorities for the safety review of food flavouring ingredients (see section 2.1).

The Committee noted that none of the previously evaluated long-term or carcinogenicity studies met modern standards in that fewer animals per group had been used than would be the present norm.

Accordingly, it reduced the previous ADI to 0–5 mg per kg of body weight, and made it temporary. The Committee requested submission, by 1992, of the results of an adequate short-term study in rats and metabolic studies in rats.

A toxicological monograph was prepared.

The existing specifications for ethyl vanillin were revised.

Fumaric acid

Fumaric acid and sodium fumarate were evaluated for the purpose of establishing an ADI by the Committee at its tenth, eighteenth, and twenty-third meetings (Annex 1, references *13, 35,* and *50*). At the eighteenth meeting, the previous unconditional ADI for fumaric acid was confirmed as an ADI of 0–6 mg per kg of body weight. At the twenty-third meeting, the Committee decided to establish a group ADI for fumaric acid and its salts of 0–6 mg per kg of body weight.

Fumaric acid was placed on the agenda of the present meeting on the basis of partial application of the method for setting priorities for the safety review of food flavouring ingredients (see section 2.1).

Because fumaric acid is a normal constituent of tissues and is metabolized by the body, the Committee decided to change the previous group ADI to a group ADI "not specified" for fumaric acid and its salts, in agreement with the guidelines laid down in section 5.2.3 of *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*).

A toxicological monograph was not prepared.

The existing specifications for fumaric acid were revised.

Quinine hydrochloride

The safety of this substance was evaluated for the first time by the Committee at its present meeting. Specifications had been developed at the twenty-fourth and twenty-sixth meetings (Annex 1, references *53* and *59*).

Biochemical studies, short-term studies in rats, teratogenicity studies in rats, and mutagenicity studies were reviewed. In these

studies, no-effect levels ranged from 40 to 100 mg per kg of body weight per day. Mutagenicity studies gave negative results.

Varied complaints including headaches and transient visual problems were reported in human volunteers given doses of 100 mg of quinine hydrochloride per person per day. These findings were not confirmed in a second, controlled study using 120 mg per person per day. A third study showed electronystagmographic changes in stressed subjects for which a no-effect level of 52.5 mg of quinine per person per day was determined. The Committee concluded that an evaluation could be made on the basis of the human data. Since the toxic effects of concern were acute and reversible, and there is extensive experience of human consumption of quinine without reports of acute toxicity, except very rarely in hypersensitive individuals, the Committee saw no need to require a margin of safety. It established an acceptable intake of 52.5 mg of quinine per person per day, equivalent to an ADI of 0–0.9 mg of quinine per kg of body weight per day. However, the Committee considered that data from more extensive human studies should be submitted and therefore made the ADI temporary.

The Committee requested submission of the results of an adequate human study by 1992.

A toxicological monograph was prepared.

The existing specifications for quinine hydrochloride were revised.

3.1.4 *Food colours*

Canthaxanthin

This substance was last evaluated by the Committee at its thirty-first meeting (Annex 1, reference *77*), when it was noted that ingestion of canthaxanthin could, in some circumstances, lead to deposits of crystals in the human retina. At that time, the Committee reduced the previously allocated ADI to 0–0.5 mg per kg of body weight and made it temporary. In addition, it required: (*a*) further details of long-term studies in rats and mice; (*b*) clarification of the factors that influence deposition in the eye, including the establishment of the threshold dose, information on the influence of dose and duration of exposure and on the reversibility of pigment accumulation, and the investigation of potential animal models; and (*c*) clarification of whether pigment deposition is causally related to impaired visual function.

Canthaxanthin is used both as a direct food additive and as a feed additive for colouring salmonid fish and chicken egg yolks. Although there is some metabolic transformation to other carotenoids in egg yolks, the parent compound is present in the products derived from animals to which it has been given as a feed additive, so the present evaluation also covers its use for this purpose.

Since the previous evaluation, substantial amounts of new data have become available and these were reviewed by the Committee.

The Committee noted that the results of two long-term carcinogenicity studies in mice and rats did not provide evidence of carcinogenicity. However, at high dose levels, canthaxanthin produced liver damage in rats (with a non-dose-related increased incidence of benign nodules in female rats); mice appeared to be less sensitive to hepatic injury. It was concluded that, in addition to the eye, the liver was a target organ for canthaxanthin.

In the long-term studies in rats, it was not possible to establish a no-effect level. However, the Committee was informed that another long-term study in rats was in progress aimed at establishing a no-effect level in respect of pathological changes in the liver.

While distribution studies with radiolabelled canthaxanthin showed that relatively high concentrations accumulated in the eye in all the mammalian species studied, crystal deposition has, to date, been observed only in the human retina. The animal species studied have therefore not provided a suitable model for the study of the pathogenesis and reversibility of this phenomenon. However, the changes noted in electroretinograms in humans were reproduced in the electroretinograms of pigmented rabbits after canthaxanthin treatment.

The Committee concluded that the long-term toxicity of canthaxanthin in rats indicated potential hepatotoxicity in humans; this matter may be resolved by obtaining clinical data from human subjects showing retinal pigment deposition. However, the Committee considered that the primary problem associated with canthaxanthin was the deposition of crystals in the human retina.

In view of the irreversibility or very slow reversibility of the retinal crystal deposition, the significance of which is not known, the Committee was unable to establish an ADI for canthaxanthin when used as a food additive or animal feed additive. The previous temporary ADI was therefore not extended.

A toxicological monograph was prepared.

The existing specifications for canthaxanthin were maintained.

Carotene preparations from natural sources

These substances were reviewed at the eighteenth and thirty-first meetings of the Committee (Annex 1, references *35* and *77*). At the latter meeting, the Committee noted that, while there was a substantial toxicological data base relating to carotenes and an ADI had been established for synthetic β-carotene, the same ADI was not applicable to natural carotenes as they did not comply with the specifications for β-carotene.

At its present meeting, the Committee considered limited biochemical, acute, and short-term toxicological studies on material derived from three different algal species, namely *Dunaliella bardawil, D. salina,* and *D. kona.* Some of the preparations produced from these species were dried concentrates produced by lyophilization or spray-drying; another product was a vegetable oil extract.

The Committee concluded that there was insufficient evidence to indicate that data relating to one species of *Dunaliella* could be applied to others. It also decided that the specifications of the test materials were so different from one another that the results of the toxicity tests could not be generalized. There were insufficient data to evaluate any of these materials for the purpose of establishing an ADI.

The Committee considered that carotene isolated from algal sources would be acceptable for food additive use if it was of sufficient purity to meet the specifications for synthetic β-carotene. Acceptance of algal biomass or crude extracts of carotene from algal sources for use as food additives would be contingent on the provision of evidence of the safety of such materials.

A toxicological monograph was not prepared.

The existing tentative specifications for carotenes (algae) were revised. The Committee was aware that three different species of *Dunaliella* are used as sources of carotene, and recognized the need for further information regarding the differences between both the species and the resulting products, and the influence of the method of manufacture, such as spray-drying, on the quality. The Committee was also informed that carbon dioxide is not used for the extraction and it saw no need to test for urethane which might have resulted from such use. The existing tentative specifications for carotenes (vegetable) were also revised. The "tentative"

qualifications for both were maintained and certain further information is required (see Annex 3).

Curcumin and turmeric oleoresin

Turmeric and curcumin (the main colouring component of turmeric) were considered at the thirteenth, eighteenth, twenty-second, twenty-sixth, and thirtieth meetings of the Committee (Annex 1, references *19, 35, 47, 59,* and *73*). Toxicological monographs were prepared on each of these occasions (Annex 1, references *20, 36, 48, 60,* and *74*). At the thirtieth meeting, the Committee concluded that turmeric is often regarded as a food rather than as a food additive, and it is therefore not appropriate to allocate an ADI to this substance. The temporary ADI for curcumin was extended, and a temporary ADI was allocated to turmeric oleoresin at that meeting.

Curcumin. When the temporary ADI of 0–0.1 mg per kg of body weight was extended at the Committee's thirtieth meeting, the submission of the results of a carcinogenicity study and a reproduction/teratogenicity study was requested. The results of these studies were not made available at the present meeting, but the Committee was informed that the results of carcinogenicity studies, including fertility assessment phases, in B6C3F1 mice and F344 rats given turmeric oleoresin containing a high concentration of curcuminoids should be available in 1990. The Committee therefore extended the temporary ADI until 1992, with the requirement that the results of the above-mentioned studies should be made available for review at that time. Since a reproduction phase is included in the ongoing carcinogenicity studies, the Committee would wish to review these studies before deciding whether the reproduction/teratogenicity study requested earlier was still needed.

A toxicological monograph was not prepared.

The existing specifications for curcumin were maintained.

Turmeric oleoresin. At the thirtieth meeting, when the Committee established the temporary ADI of 0–0.3 mg per kg of body weight for turmeric oleoresin, it requested the results of an additional short-term study in pigs or another suitable non-rodent species in order to establish a clear no-effect level for effects on the thyroid gland, which had been observed in a study in pigs. The results of such a study were

not made available at the present meeting of the Committee and the temporary ADI was therefore not extended.

A toxicological monograph was not prepared.

The Committee reviewed the specifications for turmeric oleoresin and turmeric colour as recommended at the thirtieth meeting. The Committee, at that meeting, had suggested that the specifications for turmeric oleoresin be revised to bring them into line with those for turmeric colour. However, at its present meeting, the Committee concluded that specifications for turmeric colour were contained in those for the oleoresin, and therefore deleted the existing separate specifications for the former. The specifications for turmeric oleoresin were revised to emphasize the principal colouring components of the oleoresin and to incorporate the method of assay for content of total colouring matter that was previously part of the turmeric colour specifications.

The Committee pointed out that the revised specifications for turmeric oleoresin cover a range of products, some of which are used as colours and some as flavourings; components other than pure colouring principles (e.g., the volatile oils) should therefore be taken into account, as necessary, when such products are evaluated.

Paprika oleoresin

Paprika oleoresin was evaluated at the fourteenth meeting of the Committee (Annex 1, reference *22*), when no ADI was established because it was recognized that the use of this spice extract is self-limiting for technological and organoleptic reasons.

The Committee was informed that the extraction solvent 1,2-dichloroethane is being used to produce paprika oleoresin. At both the thirty-first meeting (Annex 1, reference *77*) and the present one, the Committee revised the specifications for paprika oleoresin but decided not to include 1,2-dichloroethane as an additional processing solvent. The toxicological data on 1,2-dichloroethane were therefore not reviewed, and a toxicological monograph was not prepared.

In addition to 1,2-dichloroethane, two other chlorinated hydrocarbons are among the solvents currently listed for use in paprika oleoresin production. The Committee expressed its general opinion that levels of residues resulting from the use of any solvent should be both the minimum technically feasible and of no toxicological concern.

In future reviews of the specifications for paprika oleoresin and other oleoresins, justification by the industry for the use of chlorinated hydrocarbon solvents will be sought, together with specific information on actual residues resulting from their use.

3.1.5 *Thickening agents*

Gum arabic

This substance was last evaluated at the twenty-sixth meeting of the Committee (Annex 1, reference *59*) and an ADI "not specified" was allocated.

At its present meeting the Committee reviewed further findings from teratogenicity and biochemical studies, and concluded that the results of these studies gave no reason to modify the previous evaluation. The Committee therefore confirmed the ADI "not specified". An addendum to the existing toxicological monograph was prepared.

The Committee's attention was drawn to the fact that products were being sold as gum arabic that were derived from species other than *Acacia senegal* (L) Willdenow and closely related species hitherto recognized as the source species of gum arabic. It was informed that all these gums would be covered by the existing specifications for gum arabic.

However, the Committee was also informed of extensive studies on the chemical composition of individual gums. These studies clearly showed that, while the composition of gums from *Acacia senegal* and closely related species originating from various geographical regions varied only slightly, there were significant differences in the composition of gums from other species, for example in the carbohydrate content and ratios of different amino acids.

The existing specifications were therefore revised to reflect more closely the gums that have been toxicologically evaluated.

Modified celluloses

Modified celluloses were reviewed at the fifth, seventh, tenth, thirteenth, seventeenth, twenty-sixth, twenty-seventh, and thirtieth meetings of the Committee (Annex 1, references *5, 7, 13, 19, 32, 59, 62,* and *73*). At the seventeenth meeting, a group ADI of 0–25 mg per kg of body weight was allocated for the five modified celluloses previously reviewed (methyl cellulose, methyl ethyl cellulose,

hydroxypropyl cellulose, hydroxypropyl methyl cellulose, and sodium carboxymethyl cellulose). A toxicological monograph on these five compounds was prepared (Annex 1, reference *33*).

At the twenty-sixth and twenty-seventh meetings of the Committee, ethyl cellulose and ethyl hydroxyethyl cellulose, respectively, were reviewed and it was decided that the group ADI of 0–25 mg per kg of body weight should also apply to them. A toxicological monograph on ethyl hydroxyethyl cellulose was prepared (Annex 1, reference *74*).

Since the previous evaluation, additional data have become available, including data from studies in rats on caecal enlargement and changes in caecal flora, teratogenicity, and development, and from *in vitro* mutagenicity studies on methyl cellulose and carboxymethyl cellulose. These studies confirmed the conclusion reached at the earlier meetings of the Committee that modified celluloses are of low toxicity.

In long-term/carcinogenicity studies on hydroxypropyl methyl cellulose, methyl cellulose, methyl ethyl cellulose, and sodium carboxymethyl cellulose in rats and mice, no evidence of mutagenicity or carcinogenicity was observed. In addition, in reproduction and teratogenicity studies in mice, rats, and rabbits, the consumption of hydroxypropyl cellulose, methyl cellulose, or sodium carboxymethyl cellulose did not interfere with the reproductive process, and no embryotoxic or developmental effects were observed.

A new substantial body of human data was available on the laxative effects of modified celluloses, which are seen in some subjects at levels as low as 5 g per person per day. At higher doses, diarrhoea was reported in some subjects, but in others constipation developed. The amounts ingested in studies in humans did not exceed 30 g per person per day, which has been recommended by the United States National Research Council as the upper safe level of dietary fibre in general (*11*).

The Committee allocated a group ADI "not specified" to these modified celluloses, and pointed out that their laxative properties should be taken into account when they are used as food additives (see section 2.2.3).

A toxicological monograph was prepared.

None of the existing specifications for modified celluloses were reviewed.

3.1.6 *Miscellaneous food additives*

Ferrous lactate

Ferrous lactate, a colour adjunct, was considered for the first time by the Committee.

At the seventeenth meeting, the Committee evaluated lactic acid and its ammonium, calcium, potassium, and sodium salts (Annex 1, reference *32*). Since lactic acid is a normal constituent of food and a normal intermediary metabolite in humans, the Committee decided at that meeting to establish a "not limited" ADI.

Iron was evaluated at the twenty-seventh meeting of the Committee and, on the basis of the data available, a provisional maximum tolerable daily intake (PMTDI) of 0.8 mg per kg of body weight was allocated (Annex 1, reference *62*). It was pointed out that the tolerable daily intake should not be used as a guideline in the fortifying of processed food (Annex 1, reference *60*, section 2.8).

At its present meeting, the Committee concluded that, because the iron in ferrous lactate is bioavailable, the amount of iron resulting from the use of ferrous lactate should be included with that from all other sources, and the total should not exceed the PMTDI for iron of 0.8 mg per kg of body weight.

A toxicological monograph was not prepared.

New specifications for ferrous lactate were prepared.

2-Nitropropane

2-Nitropropane was considered by the Committee at the twenty-third, twenty-fifth, and twenty-eighth meetings (Annex 1, references *50, 56*, and *66*). Toxicological monographs were prepared after each meeting (Annex 1, references *51, 57,* and *67*). At the twenty-eighth meeting, 2-nitropropane was considered to be temporarily acceptable for use as a fractionating solvent in the production of fats and oils, as long as its use continued to be limited and residue levels were kept to the lowest technically attainable.

The Committee noted that fractionated fats and oils have physical properties that limit their application and that present procedures for the processing of fats and oils with 2-nitropropane do not lead to detectable levels of this substance in the finished product. On the assumption that such treated fats and oils may contain 2-nitropropane at the limit of detection, namely, 10 µg/kg, and on the basis of a maximum projected intake of this substance in processed oils in the United States, the maximum intake of 2-nitropropane was

estimated to be 0.13 ng per kg of body weight per day. The Committee recognized that this was a worst-case intake estimate and that actual intakes of 2-nitropropane were probably lower.

The Committee reviewed a new inhalation study in which mice were exposed to 2-nitropropane; nodular hyperplasia of the liver was observed in females. A carcinogenic effect had previously been noted in rats after inhalational exposure to relatively high concentrations (100–800 mg/m^3) of 2-nitropropane (Annex 1, reference *66*). In addition, the Committee reviewed a new study in which all rats dosed by gavage with 2-nitropropane at a level of 89 mg per kg of body weight for 16 weeks (three days per week) developed hepatocarcinomas.

On the basis of these studies, 2-nitropropane was considered to be a potent liver carcinogen in rats, and the temporary acceptance of this substance for use as a fractionating solvent in the production of fats and oils was therefore not extended. However, if the technological need for this solvent could be demonstrated and if data were provided that could be used for establishing a safe level of intake of 2-nitropropane, the Committee would reconsider it at a future meeting.

A toxicological monograph was prepared.

The existing specifications for 2-nitropropane were revised, but maintained as tentative (see Annex 3).

Tannic acid

Tannic acid was reviewed at the fifth, tenth, fourteenth, and thirty-first meetings of the Committee (Annex 1, references *5, 13, 22,* and *77*).

At the thirty-first meeting (Annex 1, reference *77*), the previous temporary ADI was changed to a temporary ADI "not specified" for tannic acid used as a filtering aid. Further data were requested on the composition of tannic acid from different sources.

Information was provided to the Committee at its present meeting that permitted revision of the specifications so as to require a high degree of purity for tannic acid used as a filtering aid where the application of good manufacturing practice ensures that it is removed from food after use. An ADI "not specified" for this use was therefore established.

As detailed information on the composition of tannic acid from different botanical sources was not forthcoming and no new

toxicological data were available, it was not possible to consider its use as a direct food additive.

A toxicological monograph was not prepared.

The Committee received updated information on the manufacture of tannic acid and, as stated above, was in a position to revise the existing tentative specifications. It maintained the "tentative" qualification and renewed the request for data on the composition of tannic acid from different botanical sources. Data on actual uses and levels of use of tannic acid as a flavouring agent were also requested (see Annex 3).

Lactoperoxidase/thiocyanate/hydrogen peroxide system

At the twenty-ninth meeting (Annex 1, reference *70*), the Committee considered the practice of adding sodium thiocyanate and hydrogen peroxide (the lactoperoxidase/thiocyanate/hydrogen peroxide system) to raw milk to maintain its quality. Since then, the Joint FAO/WHO Committee of Government Experts on the Code of Principles concerning Milk and Milk Products has produced draft guidelines for the preservation of raw milk by use of the lactoperoxidase system in circumstances where refrigeration is virtually impossible. The underlying principles and application of the lactoperoxidase system have been further elaborated in the "Code of practice for the preservation of raw milk by the lactoperoxidase system" (*12*).

The lactoperoxidase system consists of three components: lactoperoxidase naturally present in bovine and buffalo milks; added sodium thiocyanate; and an added source of hydrogen peroxide.

The Committee reviewed the draft guidelines, and noted that milk preserved by this method would contain an amount of sodium thiocyanate greater by up to 14 mg/l than that naturally present in milk.

The Committee recognized that the potential major toxic effect of thiocyanate ion is interference with iodine uptake by the thyroid gland. Thiocyanate occurs normally in blood and urine as a result of ingestion of precursors in the diet. Epidemiological studies indicate that there is no significant toxicity from chronic dietary consumption of thiocyanate provided that iodine intake is adequate.

The Committee noted that the levels of hydrogen peroxide that would be introduced into milk through the use of sodium percarbonate, a hydrogen peroxide adduct of sodium carbonate ($2Na_2CO_3.3H_2O_2$), as the source of hydrogen peroxide in the

lactoperoxidase system were lower than those considered acceptable at the twenty-fourth meeting of the Committee (Annex 1, reference *53*) and therefore were not considered to be a cause for concern. Application of the lactoperoxidase system to raw milk requires a hydrogen peroxide concentration of approximately 10 mg per litre. This is significantly lower than the concentration of hydrogen peroxide required (300–800 mg/kg) when that substance is used alone for the preservation of raw milk.

The Committee recognized that the use of the lactoperoxidase system would increase total thiocyanate exposure but considered that that would not pose any toxicological problem provided that iodine intake was adequate. It concluded that, when used according to the draft guidelines, the lactoperoxidase system does not present a toxicological hazard and, furthermore, that the system should be used in preference to hydrogen peroxide alone for the preservation of raw milk, though only where absolutely necessary, i.e., in the absence of adequate refrigeration facilities.

A toxicological monograph was not prepared.

The existing specifications for sodium thiocyanate were maintained. New specifications for sodium percarbonate were prepared.

3.2 Contaminants

3.2.1 *Patulin*

Patulin has not been previously evaluated by the Committee. The Committee noted that fungi of several different genera, including *Penicillium, Aspergillus,* and *Byssochlamys*, are capable of producing patulin. The natural occurrence of this mycotoxin has been largely associated with *Penicillium expansum*, a common spoilage microorganism in apples.

The Committee reviewed studies on the biochemistry and toxicology of patulin as well as very limited information on observations in humans when patulin was tested as an antibiotic for treatment of the common cold.

In rats, most of the administered dose was eliminated within 48 hours, in faeces and urine, less than 2% being expired as carbon dioxide. No other metabolites have been identified. About 2% of the administered dose was still present after seven days, associated primarily with erythrocytes.

Patulin has a strong affinity for sulfhydryl groups, which explains why it inhibits the activity of many enzymes. Patulin adducts formed with cysteine were less toxic than the unmodified compound in acute toxicity, teratogenicity, and mutagenicity studies.

In acute and short-term studies, patulin caused gastrointestinal hyperaemia, distension, haemorrhage, and ulceration. Pigtail monkeys tolerated patulin consumption of up to 0.5 mg per kg of body weight per day for four weeks without adverse effects.

The results of two reproduction studies in rats were available. No reproductive or teratogenic effects were noted at levels of up to 1.5 mg per kg of body weight per day, but there was an increase in the frequency of fetal resorptions at that level.

The results of a carcinogenicity study in rats, with orally administered patulin, were negative. Short-term *in vitro* genotoxicity studies indicate that patulin is not mutagenic, but it has clastogenic activity in some test systems.

The Committee set a provisional tolerable weekly intake (PTWI) for patulin of 7 µg per kg of body weight based on a no-effect level of 0.1 mg per kg of body weight per day in a combined reproduction/long-term/carcinogenicity study in rats. An additional long-term/carcinogenicity study in a rodent species other than the rat is recommended for further evaluation of the toxicity of patulin.

The Committee had before it data on patulin levels in apple juice, which is often consumed by children. On the basis of surveys in limited areas of the world, a maximum intake by children of 0.26 µg per kg of body weight per day has been estimated. However, apple juice can occasionally be heavily contaminated and the Committee therefore considered that efforts should be made to avoid unnecessary exposure to this mycotoxin by adherence to good manufacturing practices whereby rotted or mouldy fruit is not used. This should reduce dietary exposure to levels below the PTWI. The Committee urged the application of such practices.

A toxicological monograph was prepared.

3.2.2 *Polychlorinated biphenyls (PCBs)*

Polychlorinated biphenyls (PCBs) have not been previously evaluated by the Committee.

PCBs are a class of stable chlorinated hydrocarbons which, prior to the 1970s, had been used extensively in a wide range of industrial

applications. About 50–60 different PCBs, with different degrees of chlorination and thus differing physical properties, are still found in industrial products. The higher the chlorine content of PCBs, the more resistant they are to biodegradation. When PCBs are ingested, the less highly chlorinated biphenyls are metabolized in the liver, primarily to hydroxylated compounds, which are rapidly excreted. The more highly chlorinated biphenyls are more metabolically stable and accumulate in body fat.

The Committee had before it data from a large number of toxicity studies, of varying merit, most of which were carried out with commercial mixtures of PCBs. The evaluation of these studies is both difficult and complicated since the PCB mixtures tested were ill-defined and many were contaminated with polychlorinated dibenzofurans and other related chlorinated compounds. The presence of these contaminants is thought to be at least partly responsible for a number of effects seen in the animal experiments. The Committee nevertheless concluded that sufficient data were available to enable some general conclusions regarding the effects of PCBs to be reached.

Some of the PCB mixtures were hepatocarcinogenic in rodent bioassays. However, human experience from long-term accidental exposures and from epidemiological studies of workers exposed occupationally is inconclusive in respect of an association between PCB exposure and increased cancer mortality.

From a comparison of data from animal studies and symptoms observed in accidentally exposed human populations, the monkey appears to be the most appropriate animal for use in studies on PCBs. The Committee concluded, on the basis of the available studies with monkeys, that 0.04 mg per kg of body weight per day was a no-effect level; only minor effects were observed at 0.1 mg per kg of body weight per day.

Because of the limitations of the available data and the ill-defined nature of the materials that were used in feeding studies, the Committee concluded that it was impossible to establish a precise numerical value for a tolerable intake for humans. In particular, the PCB mixtures used in the monkey studies cited above were not entirely the same as those to which humans are exposed in the diet. However, there is no reason to believe that humans would be more sensitive than monkeys to the effects of PCBs, and some indication of safe exposure levels can therefore be obtained from the no-effect level observed in the monkey studies.

The major foods in which contamination with PCBs is possible are fish, milk and other dairy products, and meat. Median levels in fish reported in various countries are of the order of 100 μg/kg compared with less than 20 μg/kg for other foods. An important exception is human milk, in which PCB median levels ranging from 15 to 100 μg/kg on a whole milk basis have been reported.

The dietary intake of PCBs by various populations has been estimated to range from 0.005 to 0.2 μg per kg of body weight per day. Such a wide variation in intakes can be explained not only by the type and amount of food consumed but also by the method used to estimate the dietary PCB intake. In the case of breast-fed infants, PCB intakes can be calculated to range from 2 to 12 μg per kg of body weight per day on the basis of the median levels noted previously and an average milk intake of 120 ml per kg of body weight.

In foods that contain higher levels of PCBs and/or contribute significantly to the total dietary PCB intake, preliminary studies have identified ten specific PCBs as predominant. In human breast milk, six of them account for approximately 70% of the total PCB content.

The Committee paid particular attention to the possible health consequences of the intake of PCBs by the suckling infant, but did not anticipate that adverse health effects would occur as a result of consuming breast milk. It should be kept in mind that the infant consumes breast milk for only a short period (1–2% of the total life span). In addition, the numerous benefits of breast milk, including its nutritional, immunological, and other properties, and the psychological advantages of breast-feeding should not be discounted; the disadvantages of breast milk substitutes, including potential contamination by infective agents and the consequences of incorrect preparation and inadequate hygiene, have been amply documented (*13, 14*). For these reasons, the Committee considered that the advantages to the infant of breast-feeding outweighed any potential hazards due to the PCB content of breast milk, and advised that there was absolutely no justification for discouraging this practice.

The Committee was reassured by the observation that the production of PCBs has largely ceased. It is expected, therefore, that levels of PCBs in the environment and food, and consequently in breast milk, will decrease with time.

The Committee suggested that further investigations be conducted to identify the PCBs most commonly present in foods and that safety studies be carried out on them, and particularly on the more highly chlorinated ones, in order to determine their toxicological potential. Furthermore, specific studies on the impact of these PCBs on the fetus and neonate were considered to be of great importance.

The Committee considered that the intake of PCBs should be kept as low as possible. In foods in which PCBs occur, and that are nutritionally essential, attempts should be made to set limits on PCBs, in particular for the most highly contaminated products. However, the Committee concluded that the consumption of PCBs at the dietary levels described above did not involve any long-term hazard. Finally, the Committee pointed out that good public health practices would require that a long-term goal should be the reduction of PCBs in the diet to a minimum.

An early draft of a document on PCBs that is being prepared for publication by WHO in the Environmental Health Criteria series was made available to the Committee. The working paper on which the Committee relied for its evaluation reproduced the discussion of the metabolism and toxicity studies contained in this draft document. In order to avoid duplication within WHO, a toxicological monograph was not prepared.

4. REVISION OF CERTAIN SPECIFICATIONS

4.1 General

Four substances were evaluated for specifications only (see Annex 2), and the specifications for all of them were revised.

The Committee revised the specification for carob bean gum so as to include the use of two solvents, ethanol and isopropanol, in a washing process used to purify the substance.

The previous specifications for citric and fatty acid esters of glycerol (Annex 1, reference *75*) had been designated as "tentative" because a suitable assay method and data on the amounts of individual components were lacking. The Committee revised the tentative specifications by including analytical methods and by specifying total citric acid, total fatty acids, and total glycerol. Consideration was also given to the sum of these components,

but the Committee decided not to specify it. The "tentative" qualification was deleted.

The existing specifications for iron oxides used as food colours were revised.

The specifications for modified starches (Annex 1, reference *79*) had been designated "tentative" as analytical methods were needed for carboxyl groups in oxidized starch and free adipic acid in acetylated distarch adipate. The Committee revised the specifications to include analytical methods for both and removed the "tentative" qualification.

4.2 General specifications for enzymes used in food processing

The existing general specifications for enzyme preparations used in food processing (Annex 1, reference *69*) were revised. The Committee recommended that, as and when enzyme preparations are reconsidered, or when new enzyme preparations are submitted for evaluation, their individual specifications should be reviewed to ensure they are consistent with the principles on which the new general specifications are based.

5. FUTURE WORK

1. The guidelines for the evaluation of various groups of food additives and contaminants that have been developed by the Committee and are given in Annex 3 of *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*) should be reviewed at a future meeting (see section 2.2.1).

2. Individual specifications for enzyme preparations used in food processing should be reviewed to take account of the principles set out in the revised general specifications (see section 4.2).

3. In view of the decision not to include the use of 1,2-dichloroethane as an extraction solvent in the specifications for paprika oleoresin despite its current listing for other spice oleoresins, the Committee should re-evaluate the toxicological basis for the listing of 1,2-dichloroethane in other specifications. Such a re-examination should be expanded to include a consideration of all solvent uses of chlorinated hydrocarbons.

4. A number of the specifications reviewed at the present meeting make reference to the general methods section of the *Guide to*

specifications (Annex 1, reference *65*). The Committee reiterated the need expressed at its thirtieth and thirty-third meetings to update the general methods and to include with them in a single publication the additional general methods adopted since the last revision of this compendium.

5. During its evaluation of specifications, the Committee noted that some of them had stood for a number of years without review or revision. All such long-standing specifications should be reviewed to ensure that they reflect current practices in the additive-manufacturing and food-processing industries, and that the methods of analysis remain appropriate in the light of modern developments in analytical techniques.

6. During the evaluation of specifications for several naturally occurring substances, the Committee recognized that many of them tended to be too broad to provide an effective basis for toxicological evaluation. It therefore recognized the need to develop new principles for establishing adequate specifications that would address this problem (see section 2.3.3).

7. In a number of specifications, gas chromatography using headspace sampling is given as the method of analysis. As this technique is not included in the general methods section of the *Guide to specifications* (Annex 1, reference *65*), the Committee should develop an appropriate general method.

8. General methods should be established for laying down microbiological criteria in specifications for food additives.

6. RECOMMENDATIONS

1. In view of the large number of food additives and contaminants requiring evaluation or re-evaluation, meetings of the Joint FAO/WHO Expert Committee on Food Additives should continue to be held regularly.

2. *Patulin*

(*a*) In many of the older studies on patulin levels in fruit and fruit products, methods were used that were of inadequate sensitivity and patulin was not positively identified. There is a need to expand the current limited data base on patulin levels in such products. In particular, to ensure that reliable data on levels of patulin in apple juice and other fruit products are available for

the assessment of dietary exposure, the Committee urged the application of appropriate analytical procedures that include confirmatory techniques.

(*b*) In view of the well established association between patulin occurrence and rotted fruit:

—the sorting out of rotted apples in accordance with good manufacturing practices should be emphasized in the industrial processing of apples; and

—educational programmes for consumers should highlight the need to remove visibly damaged parts of fruit prior to consumption and to avoid consuming visibly mouldy homogeneous products such as fruit jam.

3. *Polychlorinated biphenyls (PCBs)*

(*a*) There is a need to continue monitoring PCB levels in foods and, in particular, to determine the specific PCB isomers of individual congeners. To ensure the adequacy of analytical procedures and thus the availability of more reliable data on dietary exposure for risk assessment purposes, interlaboratory check-sample programmes are considered desirable. In the light of ongoing activities related to PCBs in human milk (see section 2.4), additional efforts should be made to determine the contribution of other important foods to the dietary intake of PCBs.

(*b*) Because of advances in the analytical determination of PCBs, it is now possible to ascertain which PCB isomers of individual congeners are most prevalent in the media being examined. Once the toxicity of these PCB isomers is known, a better assessment of their human health significance will be possible. In view of the foregoing:

—Future analytical studies should be aimed at identifying and quantifying the specific isomers that are major contributors to the overall dietary intake of PCBs.

—Safety studies should be carried out on the PCBs predominantly present in foods, and particularly on the more highly chlorinated ones, in order to determine their precise toxicological potential. Furthermore, specific studies on the impact of these PCBs on the fetus and neonate are considered to be of great importance.

4. To facilitate its review of solvent specifications, as suggested at its thirtieth meeting, the Committee recommends that the relevant

industries should be requested to provide justification for the use of solvents, together with data on typical levels of residues resulting from their use. Emphasis should be placed initially on chlorinated hydrocarbon solvents.

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Annex 1

REPORTS AND OTHER DOCUMENTS RESULTING FROM PREVIOUS MEETINGS OF THE JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES

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54. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 15, 1980.
55. *Specifications for identity and purity of food additives (sweetening agents, emulsifying agents, and other food additives).* FAO Food and Nutrition Paper, No. 17, 1980.
56. *Evaluation of certain food additives* (Twenty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 669, 1981.
57. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 16, 1981.
58. *Specifications for identity and purity of food additives (carrier solvents, emulsifiers and stabilizers, enzyme preparations, flavouring agents, food colours, sweetening agents, and other food additives).* FAO Food and Nutrition Paper, No. 19, 1981.
59. *Evaluation of certain food additives and contaminants* (Twenty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 683, 1982.
60. *Toxicological evaluation of food additives.* WHO Food Additives Series, No. 17, 1982.

61. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 25, 1982.
62. *Evaluation of certain food additives and contaminants* (Twenty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 696, 1983, and corrigenda.
63. *Toxicological evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 18, 1983.
64. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 28, 1983.
65. *Guide to specifications—General notices, general methods, identification tests, test solutions and other reference materials.* FAO Food and Nutrition Paper, No. 5, Rev. 1, 1983.
66. *Evaluation of certain food additives and contaminants* (Twenty-eighth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 710, 1984, and corrigendum.
67. *Toxicological evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 19, 1984.
68. *Specifications for the identity and purity of food colours.* FAO Food and Nutrition Paper, No. 31/1, 1984.
69. *Specifications for the identity and purity of food additives.* FAO Food and Nutrition Paper, No. 31/2, 1984.
70. *Evaluation of certain food additives and contaminants* (Twenty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 733, 1986, and corrigendum.
71. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 34, 1986.
72. *Toxicological evaluation of certain food additives and contaminants.* Cambridge, Cambridge University Press, 1987 (WHO Food Additives Series, No. 20).
73. *Evaluation of certain food additives and contaminants* (Thirtieth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 751, 1987.
74. *Toxicological evaluation of certain food additives and contaminants.* Cambridge, Cambridge University Press, 1987 (WHO Food Additives Series, No. 21).
75. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 37, 1986.
76. *Principles for the safety assessment of food additives and contaminants in food.* Geneva, World Health Organization, 1987 (WHO Environmental Health Criteria, No. 70).
77. *Evaluation of certain food additives and contaminants* (Thirty-first report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 759, 1987, and corrigendum.
78. *Toxicological evaluation of certain food additives.* Cambridge, Cambridge University Press, 1988 (WHO Food Additives Series, No. 22).
79. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 38, 1988.
80. *Evaluation of certain veterinary drug residues in food.* (Thirty-second report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 763, 1988.
81. *Toxicological evaluation of certain veterinary drug residues in food.* Cambridge, Cambridge University Press, 1988 (WHO Food Additives Series, No. 23).

82. *Residues of some veterinary drugs in animals and foods*. FAO Food and Nutrition Paper, No. 41, 1988.
83. *Evaluation of certain food additives and contaminants* (Thirty-third report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 776, 1989.
84. *Toxicological evaluation of certain food additives and contaminants*. Cambridge, Cambridge University Press, 1989 (WHO Food Additives Series, No. 24).
85. *Evaluation of certain veterinary drug residues in food* (Thirty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 788, 1989.
86. *Toxicological evaluation of certain veterinary drug residues in food*. WHO Food Additives Series, No. 25, in press.
87. *Residues of some veterinary drugs in animals and foods*. FAO Food and Nutrition Paper, in press.

Annex 2

ACCEPTABLE DAILY INTAKES, OTHER TOXICOLOGICAL INFORMATION, AND INFORMATION ON SPECIFICATIONS

Substance	Specifications[1]	Acceptable daily intake (ADI) for humans and other toxicological recommendations
A. Food additives		
Emulsifiers		
Polyglycerol esters of fatty acids	S	0–25 mg/kg of body weight[2]
Sucrose esters of fatty acids	R	0–10 mg/kg of body weight[3]
Sucroglycerides	S	0–10 mg/kg of body weight[3]
Enzyme preparations		
Enzymes derived from *Aspergillus niger*	S	ADI "not specified"[4]
Flavouring agents		
Benzyl acetate	S	0–5 mg/kg of body weight[5]
Cinnamaldehyde	S	No ADI allocated[6]
Dihydrocoumarin	N, T	No ADI allocated[7]
Ethyl vanillin	R	0–5 mg/kg of body weight[5]
Fumaric acid	R	ADI "not specified"[4, 8]
Quinine	R	0–0.9 mg/kg of body weight[5]
Food colours		
Canthaxanthin	S	No ADI allocated[9]
Carotene preparations from natural sources	R, T[10]	No ADI allocated[11]
Curcumin	S	0–0.1 mg/kg of body weight[5]
Paprika oleoresin	R	No ADI allocated[12]
Turmeric oleoresin	R	No ADI allocated[9]
Thickening agents		
Gum arabic	R	ADI "not specified"[4]
Modified celluloses	S	ADI "not specified"[4, 13]
Miscellaneous food additives		
Ferrous lactate	N	[0.8 mg/kg of body weight[14]]
2-Nitropropane	R, T	No ADI allocated[15]
Tannic acid	R, T	ADI "not specified"[4, 16]
Lactoperoxidase/thiocyanate/hydrogen peroxide system for milk preservation	[17]	Acceptable[18]

Substance	Provisional tolerable weekly intake (PTWI) for humans
B. Contaminants	
Patulin	7 µg/kg of body weight
Polychlorinated biphenyls (PCBs)	PTWI not established[19]

Substance	Specifications[1]
C. Food additives (specifications only)	
Carob bean gum	R
Citric and fatty acid esters of glycerol	R
Iron oxides used as food colours	R
Modified starches	R

Notes to Annex 2

1. N, new specifications prepared; R, existing specifications revised; S, specifications exist, revision not considered or not required; and T, the existing, new, or revised specifications are tentative and comments are invited (see Annex 3).
2. Applies to polyglycerol esters of fatty acids having an average chain length of up to three glycerol units.
3. Group ADI for sucrose esters of fatty acids and sucroglycerides.
4. ADI "not specified" means that, on the basis of the available data (chemical, biochemical, toxicological, and other), the total daily intake of the substance, arising from its use at the levels necessary to achieve the desired effect and from its acceptable background in food, does not, in the opinion of the Committee, represent a hazard to health. For that reason, and for the reasons stated in the individual evaluations, the establishment of an ADI expressed in numerical form is not deemed necessary.
5. Temporary acceptance (see Annex 3).
6. The previous temporary ADI was not extended (see Annex 3).
7. See Annex 3.
8. Group ADI for fumaric acid and its salts.
9. The previous temporary ADI was not extended.
10. Specifications apply to carotenes from algal and vegetable sources (see Annex 3).
11. Insufficient information was available on toxicity and/or chemical composition to permit establishment of an ADI.
12. Self-limiting as a spice extract.
13. Group ADI for ethyl cellulose, ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, methyl ethyl cellulose, and sodium carboxymethyl cellulose. The ability of modified celluloses to produce laxative effects should be taken into account when they are used as food additives.
14. Provisional maximum tolerable daily intake for iron from all sources.

15. The previous temporary acceptance of 2-nitropropane as a fractionating solvent in the production of fats and oils was not extended.
16. For use as a filtering aid where the application of good manufacturing practice ensures that it is removed from food after use.
17. Existing specifications for sodium thiocyanate were maintained. New specifications for sodium percarbonate were prepared.
18. When used according to the draft guidelines produced by the Joint FAO/WHO Committee of Government Experts on the Code of Principles concerning Milk and Milk Products, this system does not present a toxicological hazard.
19. The Committee concluded that the no-effect level in studies with monkeys was 40 µg per kg of body weight per day. Because of the limitations of the available data and the ill-defined nature of the materials that were used in the feeding studies, it was impossible to establish a precise numerical value for a tolerable intake for humans. In particular, the PCB mixtures that were used in the studies with monkeys were not entirely the same as those to which humans are exposed in the diet. However, there is no reason to believe that humans would be more sensitive than monkeys to the effects of PCBs, and some indication of safe exposure levels can therefore be obtained from the no-effect level observed in the studies with monkeys.

Annex 3

FURTHER TOXICOLOGICAL STUDIES AND OTHER INFORMATION REQUIRED OR DESIRED

Flavouring agents

Benzyl acetate

Submission is required by 1993 of the results of long-term studies, already in progress, in which benzyl acetate is incorporated into the diet of mice and rats.

An *in vivo* test for chromosome damage in bone marrow is desirable.

Cinnamaldehyde

Submission of the results of a short-term feeding study in a non-rodent mammalian species and of adequate metabolic studies might be sufficient to make re-evaluation of this substance possible.

Dihydrocoumarin

The results of a short-term study in a rodent species and metabolic studies to investigate the extent of conversion to coumarin would be needed for re-evaluation of this substance.

In addition, information is required on the method of manufacture, with respect to the possible presence of residues of catalysts in the final product, and on the refractive index measured at 25 °C.

Ethyl vanillin

Submission of the results of an adequate short-term study in rats and metabolic studies in rats is required by 1992.

Quinine hydrochloride

Submission of the results of an adequate human study is required by 1992.

Food colours

Carotenes (algae)

Information is required on the source algae (e.g., on the different species used and the differences in the composition of the resulting

products), the influence of the manufacturing process, such as spray-drying, on the quality of finished powder preparations, and the technological justification for the presence of ethanol residues of up to 10%.

Carotenes (vegetable)

Information is required on the composition of commercial products and method(s) of distinguishing between carotenes (vegetable) and synthetic colours.

Curcumin

Submission is required by 1992 of the results of carcinogenicity studies, already in progress, with mice and rats given turmeric oleoresin containing a high concentration of curcuminoids.

Miscellaneous

2-Nitropropane

Information is required on the range of refractive indices of the commercial product. Confirmation is also required of the adequacy of the method of assay.

Tannic acid

Information is required on the composition of tannic acid from different botanical sources, on a test to show that condensed tannins are absent, and on actual use and levels of use of tannic acid as a flavouring agent.

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:

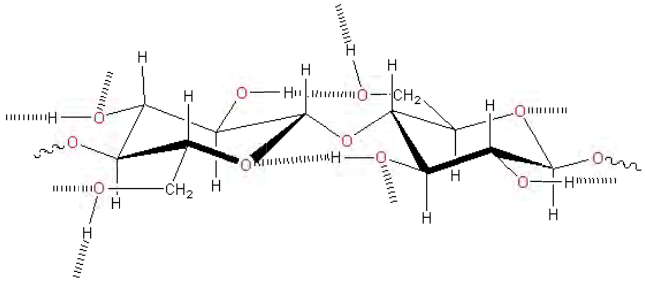
- Calcium Carboxymethyl Cellulose,
- Carboxymethyl Cellulose Acetate Butyrate,
- Carboxymethyl Hydroxyethylcellulose,
- Cellulose,
- Cellulose Acetate,
- Cellulose Acetate Butyrate,
- Cellulose Gum,
- Cellulose Acetate Propionate,
- Cellulose Acetate Propionate Carboxylate,
- Cellulose Succinate,
- Cetyl 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

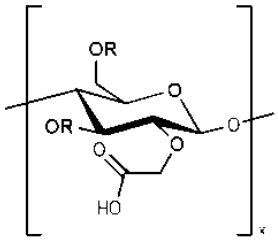
Definition and Structure

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



(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.

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.

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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SAFETY DATA SHEET

according to Regulation (EC) No. 1907/2006

Version 6.4
Revision Date 01.07.2023
Print Date 17.03.2025
GENERIC EU MSDS - NO COUNTRY SPECIFIC DATA - NO OEL DATA

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

1.1 Product identifiers

Product name	:	Hydroxypropyl cellulose
Product Number	:	435007
Brand	:	Aldrich
REACH No.	:	A registration number is not available for this substance as the substance or its uses are exempted from registration, the annual tonnage does not require a registration or the registration is envisaged for a later registration deadline.
CAS-No.	:	9004-64-2

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

Identified uses	:	Laboratory chemicals, Manufacture of substances

1.3 Details of the supplier of the safety data sheet

Company	:	Sigma-Aldrich Chemie GmbH Industriestrasse 25 CH-9471 BUCHS
Telephone	:	+41 81 755 2511
Fax	:	+41 81 756 5449
E-mail address	:	technischerservice@merckgroup.com

1.4 Emergency telephone

Emergency Phone #	:	+41 43-508-2011 (CHEMTREC) +41 44-251-5151 (Tox-Zentrum) 145(Tox Info Suisse)

SECTION 2: Hazards identification

2.1 Classification of the substance or mixture

Not a hazardous substance or mixture according to Regulation (EC) No 1272/2008.

2.2 Label elements

Not a hazardous substance or mixture according to Regulation (EC) No 1272/2008.

2.3 Other hazards

This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher.

Ecological information:
The substance/mixture does not contain components considered to have endocrine disrupting properties according to REACH Article 57(f) or Commission Delegated regulation (EU) 2017/2100 or Commission Regulation (EU) 2018/605 at levels of 0.1% or higher.

Toxicological information:
The substance/mixture does not contain components considered to have endocrine disrupting properties according to REACH Article 57(f) or Commission Delegated regulation (EU) 2017/2100 or Commission Regulation (EU) 2018/605 at levels of 0.1% or higher.

SECTION 3: Composition/information on ingredients

3.1 Substances

CAS-No. : 9004-64-2

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
After inhalation: fresh air.

In case of skin contact
In case of skin contact: Take off immediately all contaminated clothing. Rinse skin with water/ shower.

In case of eye contact
After eye contact: rinse out with plenty of water. Remove contact lenses.

If swallowed
After swallowing: make victim drink water (two glasses at most). Consult doctor if feeling unwell.

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

Unsuitable extinguishing media
For this substance/mixture no limitations of extinguishing agents are given.

5.2 Special hazards arising from the substance or mixture
Carbon oxides

5.3 Advice for firefighters
In the event of fire, wear self-contained breathing apparatus.

5.4 Further information
Prevent fire extinguishing water from contaminating surface water or the ground water system.

SECTION 6: Accidental release measures

6.1 Personal precautions, protective equipment and emergency procedures
Advice for non-emergency personnel: Avoid inhalation of dusts. Evacuate the danger area, observe emergency procedures, consult an expert.
For personal protection see section 8.

6.2 Environmental precautions
Do not let product enter drains.

6.3 Methods and materials for containment and cleaning up
Cover drains. Collect, bind, and pump off spills. Observe possible material restrictions (see sections 7 and 10). Take up dry. Dispose of properly. Clean up affected area. Avoid generation of dusts.

6.4 Reference to other sections
For disposal see section 13.

SECTION 7: Handling and storage

7.1 Precautions for safe handling
For precautions see section 2.2.

7.2 Conditions for safe storage, including any incompatibilities

Storage conditions
Tightly closed. Dry.

Storage class
Storage class (TRGS 510): 11: 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

Ingredients with workplace control parameters

8.2 Exposure controls

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). Safety glasses

Skin protection
This recommendation applies only to the product stated in the safety data sheet, supplied by us and for the designated use. When dissolving in or mixing with other substances and under conditions deviating from those stated in EN374 please contact the supplier of CE-approved gloves (e.g. KCL GmbH, D-36124 Eichenzell, Internet: www.kcl.de).

Full contact
Material: Nitrile rubber
Minimum layer thickness: 0,11 mm
Break through time: 480 min
Material tested:KCL 741 Dermatril® L

Splash contact
Material: Nitrile rubber
Minimum layer thickness: 0,11 mm
Break through time: 480 min
Material tested:KCL 741 Dermatril® L

Respiratory protection
required when dusts are generated.
Our recommendations on filtering respiratory protection are based on the following standards: DIN EN 143, DIN 14387 and other accompanying standards relating to the used respiratory protection system.
Recommended Filter type: Filter type P1

The entrepeneur has to ensure that maintenance, cleaning and testing of respiratory protective devices are carried out according to the instructions of the producer. These measures have to be properly documented.

Control of environmental exposure
Do not let product enter drains.

SECTION 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties

a)	Physical state	powder
b)	Color	white

c)	Odor	No data available
d)	Melting point/freezing point	No data available
e)	Initial boiling point and boiling range	No data available
f)	Flammability (solid, gas)	No data available
g)	Upper/lower flammability or explosive limits	No data available
h)	Flash point	No data available
i)	Autoignition temperature	400 °C
j)	Decomposition temperature	No data available
k)	pH	No data available
l)	Viscosity	Viscosity, kinematic: No data available Viscosity, dynamic: No data available
m)	Water solubility	No data available
n)	Partition coefficient: n-octanol/water	No data available
o)	Vapor pressure	No data available
p)	Density	0,5 g/mL at 25 °C
	Relative density	No data available
q)	Relative vapor density	No data available
r)	Particle characteristics	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
The product is chemically stable under standard ambient conditions (room temperature) .

10.3 Possibility of hazardous reactions
No data available

10.4 Conditions to avoid
no information available

10.5 Incompatible materials
Strong oxidizing agents

10.6 Hazardous decomposition products
In the event of fire: see section 5

SECTION 11: Toxicological information

11.1 Information on toxicological effects

Acute toxicity
LD50 Oral - Rat - 10.200 mg/kg
Remarks: (RTECS)
Inhalation: No data available
Dermal: No data available

Skin corrosion/irritation
No data available

Serious eye damage/eye irritation
No data available

Respiratory or skin sensitization
No data available

Germ cell mutagenicity
No data available

Carcinogenicity
No data available

Reproductive toxicity
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

11.2 Additional Information

Endocrine disrupting properties

Product:

Assessment	The substance/mixture does not contain components considered to have endocrine disrupting properties according to REACH Article 57(f) or Commission Delegated regulation (EU)

2017/2100 or Commission Regulation (EU) 2018/605 at levels of 0.1% or higher.

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
This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher.

12.6 Endocrine disrupting properties

Product:

Assessment	:	The substance/mixture does not contain components considered to have endocrine disrupting properties according to REACH Article 57(f) or Commission Delegated regulation (EU) 2017/2100 or Commission Regulation (EU) 2018/605 at levels of 0.1% or higher.

12.7 Other adverse effects
No data available

SECTION 13: Disposal considerations

13.1 Waste treatment methods

Product
See www.retrologistik.com for processes regarding the return of chemicals and containers, or contact us there if you have further questions.

SECTION 14: Transport information

14.1 UN number
ADR/RID: - IMDG: - IATA: -

14.2 UN proper shipping name
ADR/RID: Not dangerous goods

IMDG: Not dangerous goods
IATA: Not dangerous goods

14.3 Transport hazard class(es)

ADR/RID: - IMDG: - IATA: -

14.4 Packaging group

ADR/RID: - IMDG: - IATA: -

14.5 Environmental hazards

ADR/RID: no IMDG Marine pollutant: no IATA: no

14.6 Special precautions for user

No data available

Further information

Not classified as dangerous in the meaning of transport regulations.

SECTION 15: Regulatory information

15.1 Safety, health and environmental regulations/legislation specific for the substance or mixture

This material safety data sheet complies with the requirements of Regulation (EC) No. 1907/2006.

International Chemical Weapons Convention (CWC) Schedules of Toxic Chemicals and Precursors	:
Restrictions on the marketing and use of certain dangerous substances and preparations	:
Regulation (EC) No 649/2012 of the European Parliament and the Council concerning the export and import of dangerous chemicals	:
Candidate List of Substances of Very High Concern for Authorisation	:

15.2 Chemical Safety Assessment

For this product a chemical safety assessment was not carried out

SECTION 16: Other information

Full text of other abbreviations

ADN - European Agreement concerning the International Carriage of Dangerous Goods by Inland Waterways; ADR - Agreement concerning the International Carriage of Dangerous Goods by Road; AIIC - Australian Inventory of Industrial Chemicals; ASTM - American Society for the Testing of Materials; bw - Body weight; CMR - Carcinogen, Mutagen or Reproductive Toxicant; DIN - Standard of the German Institute for Standardisation; DSL - Domestic Substances List (Canada); ECx - Concentration associated with x% response; ELx - Loading rate associated with x% response; EmS - Emergency Schedule; ENCS - Existing and New Chemical Substances (Japan); ErCx - Concentration associated with x% growth rate response; GHS - Globally Harmonized System; GLP - Good Laboratory Practice; IARC - International Agency for Research on Cancer; IATA - International Air Transport Association; IBC - International Code for the Construction and Equipment of Ships carrying Dangerous Chemicals in Bulk; IC50 - Half maximal inhibitory concentration; ICAO - International Civil Aviation Organization; IECSC - Inventory of Existing Chemical Substances in China; IMDG - International Maritime Dangerous Goods; IMO - International Maritime Organization; ISHL - Industrial Safety and Health Law (Japan); ISO - International Organisation for Standardization; KECI - Korea Existing Chemicals Inventory; LC50 - Lethal Concentration to 50 % of a test population; LD50 - Lethal Dose to 50% of a test population (Median Lethal Dose); MARPOL - International Convention for the Prevention of Pollution from Ships; n.o.s. - Not Otherwise Specified; NO(A)EC - No Observed (Adverse) Effect Concentration; NO(A)EL - No Observed (Adverse) Effect Level; NOELR - No Observable Effect Loading Rate; NZIoC - New Zealand Inventory of Chemicals; OECD - Organization for Economic Co-operation and Development; OPPTS - Office of Chemical Safety and Pollution Prevention; PBT - Persistent, Bioaccumulative and Toxic substance; PICCS - Philippines Inventory of Chemicals and Chemical Substances; (Q)SAR - (Quantitative) Structure Activity Relationship; REACH - Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals; RID - Regulations concerning the International Carriage of Dangerous Goods by Rail; SADT - Self-Accelerating Decomposition Temperature; SDS - Safety Data Sheet; TCSI - Taiwan Chemical Substance Inventory; TECI - Thailand Existing Chemicals Inventory; TSCA - Toxic Substances Control Act (United States); UN - United Nations; UNRTDG - United Nations Recommendations on the Transport of Dangerous Goods; vPvB - Very Persistent and Very Bioaccumulative

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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