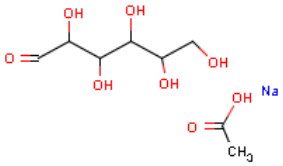
Sodium carboxymethyl cellulose

Ingredient synonym names

Cellulose carboxymethyl ether, sodium, CMC sodium salt, Carboxymethyl cellulose, sodium salt, Cellex, Aquacide I, Calbiochem, Aquacide II, Calbiochem, Cellulose gum, 7H3SF, AC-Di-sol. NF, Aku-W 515, Aquaplast, Avicel RC/CL, B 10, B 10 (Polysaccharide), Blanose BS 190, Blanose BWM, CM-Cellulose sodium salt, CMC, CMC 2, CMC 3M5T, CMC 41A, CMC 4H1, CMC 4M6, CMC 7H, CMC 7H3SF, CMC 7L1, CMC 7M, CMC 7MT, CMC sodium salt, Camellose gum, Carbose 1M, Carboxymethylcellulose sodium, Carboxymethylcellulose sodium salt, Carmellose gum, Carmellose sodium, low-substituted, Carmethose, Cellofas, Cellofas B, Cellofas B5, Cellofas B50, Cellofas B6, Cellofas C, Cellogel C, Cellogen 3H, Cellogen PR, Cellogen WS-C, Cellpro, Cellufix FF 100, Cellufresh, Cellugel, Cellulose carboxymethyl ether sodium salt, Cellulose glycolic acid, sodium salt, Cellulose gum, Cellulose sodium glycolate, Cellulose, carboxymethyl ether, sodium salt, low-substituted, Celluvisc, Collowel, Copagel PB 25, Courlose A 590, Courlose A 610, Courlose A 650, Courlose F 1000G, Courlose F 20, Courlose F 370, Courlose F 4, Courlose F 8, Daicel 1150, Daicel 1180, Edifas B, Ethoxose, Fine Gum HES, Glikocel TA, KMTs 212, KMTs 300, KMTs 500, KMTs 600, Lovosa, Lovosa 20alk., Lovosa TN, Lucel (polysaccharide), Majol PLX, Modocoll 1200, NaCm-cellulose salt, Nymcel S, Nymcel ZSB 10, Nymcel ZSB 16, Nymcel slc-T, Polyfibron 120, S 75M, Sanlose SN 20A, Sarcell tel, Sodium CM-cellulose, Sodium CMC, Sodium carboxmethylcellulose, Sodium carboxymethyl cellulose, Sodium carboxymethylcellulose, Sodium cellulose glycolate, Sodium glycolate cellulose, Sodium salt of carboxymethylcellulose, Tylose 666, Tylose C, Tylose C 1000P, Tylose C 30, Tylose C 300, Tylose C 600, Tylose CB 200, Tylose CB series, Tylose CBR 400, Tylose CBR series, Tylose CBS 30, Tylose CBS 70, Tylose CR, Tylose CR 50, Tylose DKL, UNII-K679OBS311, Unisol RH

IDENTIFIER DETAILS

Ingredient chemical structure



CAS Number	FEMA Number	Additive Number	Ingredient EC Number
9004-32-4	-	E467	-

CAS Additional Number	FL Number	CoE Number
-	-	-

Chemical formula: C2H4O3.xNa. x-Unspecified

Ingredient CLP Classification

Ingredient REACH Registration Number

-

Acute Oral Toxicity	Eye Damage/Irritation	Carcinogenity
0	0	0

Acute Dermal Toxicity	Respiratory Sensitisation	Reproductive Toxicity
0	0	0

Acute Inhalation Toxicity	Skin Sensitisation	Aspiration Toxicity

Sodium carboxymethyl cellulose

0	0	0
Skin Corrosive/Irritant	Mutagenicity/ Genotoxicity	Specific Target Organ Toxicity
0	0	0

SPECIFICATIONS

Melting Point	-	Boiling Point	-

STATUS IN FOOD AND DRUG LAWS

Acceptable Daily Intake (ADI, mg/kg)	Not Specified (JECFA, 1989)
Acceptable Daily Intake (ADI) comments	In 2018 The EFSA ANS 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. The Panel considered an indicative total exposure of around 660–900 mg/kg bw per day for microcrystalline, powdered and modified celluloses.
FDA Status	CFR21 184.1745 (0.5% - 5.0%) 582.174 5S ubstances generally recognised as safe

CoE limits - Beverages (mg/kg)	-	CoE limits - Food (mg/kg)	-	CoE limits - Exceptions (mg/kg)	-

HUMAN EXPOSURE

Ingredient Natural Occurence (if applicable)

No data identified.

References - Ingredient Natural Occurence

No data identified.

Ingredient Reported Uses

Sodium carboxymethyl cellulose is used in a wide variety of applications including as a thickening agent in food, cosmetic products, toothpaste, detergents, used in oil drilling, used to make suspensions and/or tablets of pharmaceutical products [e.g. Anonymous 1986; Cornelis et al., 1995; Lewis et al., 1997].
Carboxymethyl cellulose (CMC) is a water-soluble semi-synthetic polymer in which some of the groups of cellulose have been replaced at random by carboxymethyl groups. The average number of carboxymethyl groups per glucose unit is denoted by the degree of substitution. CMC with a degree of substitution ranging between 0.4-1.3 has become the most commonly used [Cornelis et al., 1995].

References - Ingredient Reported Uses

Cornelis et al., (1995) The biodegradability and nontoxicity of carboxymethyl cellulose (DS 0.7) and intermediates. Environmental & Toxicology Chemistry. 15(3): 270-274.

TOXICITY DATA

In Vivo Data

Acute Toxicity Data

Reported as: Species - Test Type - Route Reported - Dosage - [Reference]
Rat - LD50 - Oral - 15-27g/kg - [Selanski et al., 1948]
Pig - LD50 - Oral - 16g/kg - [Selanski et al., 1948]
Guinea Pig - LD50 - Oral - 16000mg/kg - [ToxNet, 2010]
Mouse - LD50 - Oral - >2700mg/kg - [ToxNet, 2010]
Rabbit - LD50 - Oral - >2700mg/kg - [ToxNet, 2010]
Rabbit - LD50 - Dermal - >2700mg/kg - [ToxNet, 2010]
Rat - LD50 - Dermal - >2700mg/kg - [ToxNet, 2010]
Rat - LC50 - Inhalation - >5800mg/m2 - [ToxNet, 2010]

References
Shelanski et al., (1948) Food Research. 13: 29 (As cited in JECFA 1990).
ToxNet, searched 2010. http://toxnet.nlm.nih.gov/

In Vivo Carcinogenicity/Mutagenicity

A group of thirty rats were given an injection of 1 ml of 2 % aqueous solution of CMC subcutaneously once a week. After 10 months 43 % of the rats had fibrosarcomas of moderate malignancy at the injection site [Lusky et al., 1957]. In a similar study 20 rats were given an injection of 2% aqueous solution of CMC subcutaneously once a week. Four animals developed neoplasm's at the injection site, 2 were fibromas and two were fibrosarcomas [Jasmin, 1961].

Groups of 50 male and 50 female rats were fed for up to 100 weeks at 0, 0.1 and 1 % CMC in the diet. There was found to be no difference between any of the groups in terms of tumour incidence or mortality [Imperial Chemical Industries, 1966; McElliot et al., 1968].

Groups of 30 male and 30 female rats received (Spartan strain) received diets containing 0,1 or 5 % CMC in the diet for two years. At histopathological examination, there was no increased incidence of tumours in either group that received CMC compared to the control rats [JECFA, 1990].

In 2018 the EFSA ANS Panel concluded that their structural, physicochemical and biological similarities, allows for read-across between all the celluloses. 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 [EFSA, 2018].

References - In Vivo Carcinogenicity/Mutagenicity

Imperial Chemical Industries (1966) Unpublished reports submitted to WHO (as cited in JECFA 1974).
Jasmin et al., (1961) Storage and tissue disposal of carboxymethyl cellulose. Reviews of Canadian Biology.

JECFA (1990). 35th meeting of the Joint FAO/WHO Expert Committee on Food Additives. WHO Food Additives Series 26.

Lusky et al., (1957) Fibrosarcomas induced by multiple subcutaneous injections of carboxymethyl cellulose (CMC), polyvinylpyrrolidone (PVP), and polyoxyethylene sorbitan monostearate (Tween 60) Federal Proceedings. 16: 318.

McElliott et al., (1968) Long-term feeding studies of methylethylcellulose (Edifas A) and sodium carboxymethylcellulose (Edifas b) in rats and mice. Food & Cosmetic Toxicology. 6(4): 449-460.

EFSA ANS (2018). 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 Journal 2018, 16(1)5047

Dermal Toxicity

Daily doses of 20 – 30 g sodium carboxymethyl cellulose for 7 days were well tolerated in human subjects [Ziegelmayer et al., 1951].

Skin test on 100 men and 100 women demonstrated that CMC was neither a primary irritant or a sensitiser in any of the tests carried out [Shelanski et al., 1945]. Incidences of allergic contact dermatitis and contact urticaria has been reported in humans in contact with CMC [e.g. Hamada et al., 1978: Johnsson et al., 1999, Moreau et al., 2006].

References - Dermal Toxicity

Hamada et al., (1978) Allergic contact dermatitis due to sodium carboxylmethylcellulose. Contact Dermatitis 4(4): 244 Johnsson et al., (1999) Contact urticaria syndrome due to carboxymethylcellulose in a hydrocolloid dressing. Contact Dermatitis. 341(6): 344-345.

Moreau et al., (2006). Contact urticaria from carboxymethylcellulose in white chalk. Dermatitis. 17(1):29-31.

Shelanski et al., (1948) Food Research. 13: 29 (As cited in JECFA 1990).

Ziegelmayer et al., (1951) Arch Tier Ernähr 2:33 (as cited in JECFA 1974).

Reproductive/ Developmental Toxicity

A teratology study that administered 0.5% CMC on Day 7-19 of gestation in rabbits found no evidence for any treatment-related abnormalities [Henwood et al., 1992]. Administration of CMC at 0.1% to Sprague Dawley rats on days 6-17 of gestation failed to find any treatment-related clinical signs or fetal abnormalities [Gupta et al., 1996]. In a more recent study 1% CMC was administered to pregnant rats and rabbits by oral gavage throughout the period of organogenesis. No evidence of any developmental teratology was seen [Lewis et al., 1997].

Groups of 25 rats were maintained for 2 years on diets containing 10, 500 and 1000 mg/kg/day. For the three generations there was no evidence of any differences between the dose groups and the control animals [Shelanski et al., 1945]. Fritz et al., (1981) tested CMC orally at 2% in an aqueous solution in 20 male and 40 female albino rats to cover the entire reproductive cycle and up to day 14 of pregnancy. The authors found that there was no effect on reproductive success or development of the pups.

Concerning reproductive and developmental toxicity, data are available for microcrystalline cellulose, methyl cellulose, hydroxypropyl cellulose and sodium carboxy methyl, cellulose. The substances were tested in mice, rats, hamsters and/or rabbits with oral dosing via gavage. Adverse effects on reproductive performance or developmental effects were not observed with modified and unmodified celluloses at doses greater than 1000 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

and sodium carboxy methyl cellulose. Given the similarities in their structure, relevant physicochemical, metabolic and toxicological properties, the EFSA ANS Panel considered it possible to read-across between all the celluloses [EFSA ANS, 2018].

References - Reproductive/ Developmental Toxicity

Fritz et al., (1981) The suitability of carboxymethyl cellulose as a vehicle in reproductive studies. Drug Research 31: 813-815.

Gupta et al., (1996) Developmental toxicity testing of alternative vehicles: PEG 400, cremophore and carboxymethylcellulose: comparisons with methylcellulose. Toxicologist 30(1): 192.

Henwood et al., (1992) Time-mated rabbit teratology study. Toxicologist 12(1): 104.
Lewis et al., (1997) Evaluation of oral dosing vehicles for use in developmental toxicity studies in the rat and rabbit.
Toxicologist. 36(1): 259-260.

Shelanski et al., (1948) Food Research. 13: 29 (As cited in JECFA 1990).

EFSA ANS (2018). 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 Journal 2018, 16(1)5047.

Inhalation Toxicity

In an inhalation study six rabbits received twice daily CMC powder in one nostril. CMC was shown to inhibit ciliary beat frequency being both time and concentration dependent. CMC caused mild to moderate inflammation after 4 weeks [Ugwoke et al., 2000]. Cellulose derivatives on the whole have been reported to be practically nontoxic by the inhalation route [Anonymous, 1986].

References - Inhalation Toxicity

Anonymous (1986) Final report on the safety assessment of hydroxyethylcellulose, hydroxypropylcellulose, methylcellulose, hydroxypropyl methylcellulose and cellulose gum. TA: Journal of the American College of Toxicology. IP3 VI:5: 1-59.

Ugwoke et al., (2000). Toxicological investigations of the effects carboxymethylcellulose on ciliary beat frequency of human nasal epithelial cells in primary suspension culture and in vivo on rabbit nasal mucosa. International Journal of Pharmacology. 205(1-2): 43-51.

Cardiac Toxicity

No data identified.

References - Cardiac Toxicity

No data identified.

Addictive Data

No data identified.

References - Addictive Data

No data identified.

Behavioral data

No data identified.

References - Behavioral data

No data identified.

In Vivo - Other Relevant Studies

The administration of radio-labelled CMC containing up to 0.34 % radioactive sodium glycolate, was given orally to two groups of five male rats at 400mg. Less than 0.2% of the radio activity was found in the liver and kidney with 0.14% of the radio labelled dose ending up bin the 48 hour urine sample. The author, however the authors suggested that the free radioactive glycolate in the test CMC could account for these values [Wiebe et al., 1962]

Co administration of 1% CMC (20 ml/kg) via the intraperitoneal route prior to treatment with paracetamol and adriamycin has been demonstrated to increase the toxicity of the two compounds when dosed to mice, primarily via a decrease in hepatic glutathione. This lead to increased hepatotoxicity [Decorti et al., 1983: Klugmann et al., 1984].

IL-10 deficient mice are used as the standard model for inflammatory bowel disease (IBD) inflammation. A study using these mice investigated the effect of carboxy methyl cellulose. Mice were given 2% CMC solution (n=7) or water (n=6) orally for a period of 3 weeks. Compared to the control mice the CMC-treated mice were observed to have increased growth of bacteria both in the lumina and between the villi, and increased distensions between villi, with these areas also filled with bacteria. Furthermore the bacteria were also found adhered to the mucosa and migrating into the bottom of the crypts of Lieberkuehn. The authors concluded that 'CMC induces bacterial overgrowth and small bowel inflammation in susceptible animals' and further suggest it to be a potential suspect in the rise of IBD in the 20th century [Swidsinski et al., 2009].

References - In Vivo - Other Relevant Studies

Weibe et al., (1962) Unpublished report to the Hercules Powder Co. (As cited in JECFA 1974).

Decorti et al., (1983) Enhancement of adriamycin toxicity by carboxy methyl cellulose in mice. Toxicocology & Applied Pharmacology. 71(2): 288-293.

Klugmann et al., (1984) Enhancement of paracetamol induced hepatotoxicity by prior treatment with carboxymethylcellulose. Pharmacology Research Communications. 16(3): 313-318.

Swidsinski et al., (2009). Bacterial overgrowth and inflammation of the small intestine after carboxymethylcellulose ingestion in genetically susceptible mice. Inflamm Bowel Dis. 15(3): 359-364.

In Vitro Data

In Vitro Carcinogenicity/Mutagenicity

There was reported to be no chromosomal aberrations detected in Chinese hamster fibroblasts using concentrations of CMC up to 2.8 mg/ml [Ishidate et al., 1984].

Sodium carboxymethyl cellulose (CMC) was found to be negative in the Ames test (in the presence and absenceof a metabolic fraction), in the Salmonella typhimurium strains TA97 and TA102 at 0-10 mg/plate [Fujita et al.,1988] and in strains TA98 and TA100 [Strizhel et al., 1994].

Additional information concerning the in vitro mutagenicity and genotoxicty of this material may be found in “An Interim report on data originating from Imperial Tobacco Limited’s Genotoxicity testing programme September 2003” or “An updated report on data originating from Imperial Tobacco Limited’s external Genotoxicity testing programme – Round 2 August 2007”.

References - In Vitro Carcinogenicity/Mutagenicity

An Interim report on data originating from Imperial Tobacco Limited’s Genotoxicity testing programme September 2003 – internal document

An updated report on data originating from Imperial Tobacco Limited’s external Genotoxicity testing programme – Round 2 August 2007 – internal document

Ishidate et al., (1984) Primary mutagenicity screening of food additives currently used in Japan. Food & Cosmetic Toxicology 22: 623-628.

Strizhel chik et al., (1994) The mutagenic properties of new gelatinous substances studied using the Ames test. Tsitol Genet. 28(3): 91-93.

In Vitro - Other Relevant Studies

No data identified.

References - In Vitro - Other Relevant Studies

No data identified.

Emissions and Associated Toxicity Data

Additional information concerning the in vitro mutagenicity of this material may be found in “An Interim report on data originating from Imperial Tobacco Limited’s Genotoxicity testing programme September 2003” or “An updated report on data originating from Imperial Tobacco Limited’s external Genotoxicity testing programme – Round 2 August 2007”.

References - Emissions and Associated Toxicity Data

An Interim report on data originating from Imperial Tobacco Limited’s Genotoxicity testing programme September 2003 – internal document

An updated report on data originating from Imperial Tobacco Limited’s external Genotoxicity testing programme – Round 2 August 2007 – internal document