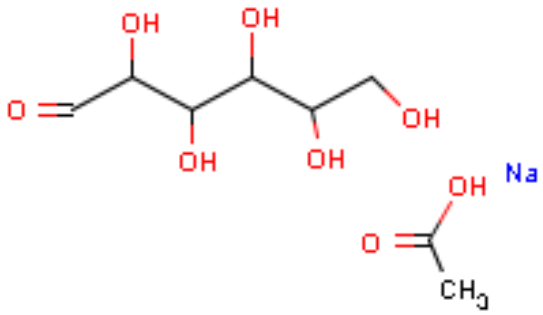
SODIUM CARBOXY METHYL CELLULOSE

SYNONYMS

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

CHEMICAL STRUCTURE



CHEMICAL FORMULA

C2H4O3.xNa. x-Unspecified

IDENTIFIER DETAILS

CAS Number	:	9004-32-4
CoE Number	:	-
FEMA	:	-
EINECS Number	:	-
E Number	:	E468 crosslinked sodium carboxymethyl cellulose

CLP CLASSIFICATION

Ingredient CLP Classification: No

Endpoint	Classification	Category
Acute Oral Toxicity	-	-
Acute Dermal Toxicity	-	-
Acute Inhalation Toxicity	-	-
Skin Corrosive/irritant	-	-
Eye Damage/Irritation	-	-
Respiratory Sensitisation	-	-
Skin Sensitisation	-	-
Mutagenicity/Genotoxicity	-	-
Carcinogenicity	-	-
Reproductive Toxicity	-	-
Specific Target Organ Toxicity	-	-
Aspiration Toxicity	-	-

SPECIFICATIONS

Melting Point: -

Boiling point: -

PURPOSE

Component

STATUS IN FOOD AND DRUG LAWS

CoE limits:

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

Acceptable Daily Intake:

ADI (mg/kg)	ADI Set by	Date Set	Comments
NOT SPECIFIED	JECFA	1989	Group ADI for modified celluloses:

			ethyl cellulose, ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose, methyl ethyl cellulose, and sodium carboxymethyl cellulose

FDA Status:(CFR21)

Section Number	Comments
184.1745	(0.5% - 5.0%)
582.1745	Substances generally recognised as safe

HUMAN EXPOSURE

Natural Occurrence: Sodium carboxymethyl cellulose does not occur in nature.

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].

TOXICITY DATA

In Vivo Toxicity Status

Species	Test Type	Route	Reported dosage
Rat	LD_{50}	Oral	15 – 27 g/kg
Pig	LD_{50}	Oral	16 g/kg [Selanski *et al.,* 1948]
Guinea Pig	LD_{50}	Oral	16000 mg/kg
Mouse	LD_{50}	Oral	> 27000 mg/kg
Rabbit	LD_{50}	Oral	> 27000 mg/kg
Rabbit	LD_{50}	Skin	> 2000 mg/kg
Rat	LC_{50}	Inhalation	> 5800 mg/m^3
Rat	LD_{50}	Oral	27000 mg/kg [ToxNet, 2010]

The administration of 50 g/kg of CMC in the diet of weanling rats for 4 weeks was found to increase the caecal wall and caecal contents significantly and

increase the activity of bacterial azoreductases, beta-glucosidases, beta-glucuronidase, nitrate reductase, nitro reductase and urease [Mallet *et al.,* 1984].

The laxative effect of sodium carboxy methyl cellulose in humans has been widely studied; up to 15 g/day was well tolerated and led to an increase in intestinal transit time. Some individuals have been found to be sensitive to doses as low as 5 g/day, whilst higher doses are associated with both diarrhoea and constipation. An intake of 30 g/day has been recommended as the upper safe level of dietary fibre in general [JECFA, 1974].

Six rats given an i.v. injection of 40 ml of a 1.6% CMC solution were reported to have particles localised in cells of the reticulo-endothelial system 48 h later [Jasmin *et al.,* 1961].

On feeding 6 rats 4, 10 and 14% CMC in the diet for 4 periods of 10 days duration, the percentage in the diet was quantitatively reclaimed in the diet. However, only 50% of the CMC administered in the diet in two rabbits at 4.76% and 9% in the diet was recovered [Ziegelmayer *et al.,* 1951].

Two human volunteers received 30 g and a third 20 g orally for 4 days, approximately 90 % of the CMC was recovered from the diet [Ziegelmayer *et al.,* 1951].

Two groups of 100 guinea pigs received CMC at 500 or 1000 mg/kg/day for six months in the diet, and two groups of 20 received CMC at 500 or 1000 mg/kg/day for 1 year. In both cases there was no evidence of toxicity in both gross pathology and histopathological investigations [Shelanski *et al.,* 1948].

Groups of 10 dogs were fed CMC at 500 or 1000 mg/kg/day in the diet for 6 months. There was no evidence of any toxicity, or in any of the tissues examined histologically [Shelanski *et al.,* 1948].

Five dogs that received 0.25 % CMC in 1% saline solution i.v. with doses increasing from 40–150 mls for 3 months, the only finding was uptake of CMC in the reticuloendothelial cells in the aorta [Hueper *et al.,* 1945]. Four dogs given an intravenous (i.v.) injection of 40 mls of 0.25 % CMC in 1 % sodium chloride solution reacted with a transitory leucopaenia [Hueper, 1945].

A group of 10 rats that received CMC at 20% of the diet for 9 weeks. A slight growth retardation and laxative effect was noted. There were no other changes in organ weights, macro or micropathology noted [Rowe *et al.,* 1944].

Rats (10 males and 15 females) given CMC as 5 % of the diet for 28-36 weeks, there was found to be no difference in organ weights or limited tissue histology between the treated and control groups [Rowe *et al.,* 1944].

Rats, guinea pigs and rabbits have been reported to show no symptoms on having received 3000 mg/kg spilt as three sub-doses by oral gavage [Rowe *et*

al., 1944].

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].

Dermal Toxicity

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

Ocular and dermal irritation demonstrate that at worst cellulose derivatives are minimally irritating to rabbit eyes and non irritating to rabbit skin when applied at concentrations up to 100 % [Anonymous, 1986].

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].

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.

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 non-toxic by the inhalation route [Anonymous, 1987].

Other Relevant Studies

Sodium CMC is readily hydrolysed by micro organisms [Reese *et al.,* 1950]. Letzig (1943) reported that the enzymes diastase and in general cellulases have the ability to breakdown CMC. Pepsin and pancreatin do not degrade CMC [Massatach *et al.,* 1940].

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].

Behavioural Data

No data identified

In Vitro Toxicity Status

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 absence of 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 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”.

Other Relevant Studies

No data identified.

PYROLYSIS AND TRANSFER STUDIES

Information relating to the pyrolysis and/or transfer of sodium carboxymethyl cellulose is detailed in the Report on Thermochemical Properties of Ingredients document. In the aforementioned document, the term ‘pyrolysis’ means the heating of an ingredient in isolation under controlled conditions in an analytical device to examine its degradation potential. The expression ‘transfer data’ on the other hand is used to describe the fate of an ingredient in qualitative and quantitative terms following the smoking of a tobacco product to which it has been applied.

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