# CELLULOSE (FIBRE)

## SYNONYMS

Bleached ground wood pulp
Cellulose chemical pulp
Cellulose cotton linter pulp
Cellulose, chemical pulp
Cellulose,chemical pulp
Chemical pulp, non-sulfur
Pulp, cellulose
Rags

## CHEMICAL STRUCTURE

The fibrous substance obtained from the treatment of lignocellulosic substances ( wood or other agricultural fibre sources) with one or more aqueous solutions of pulping and/or bleaching chemicals. Composed of cellulose, hemi-cellulose, lignin, and other minor components. The re lative amounts of these components depend on the extent of the pulping and bleaching processes.

## CHEMICAL FORMULA

Unspecified – Mixture of components

## IDENTIFIER DETAILS

| | | |
|---|---|---|
| CAS Number | : | 65996-61-4 |
| CoE Number | : | - |
| FEMA | : | - |
| EINECS Number | : | 265-995-8 |
| E Number | : | - |

## SPECIFICATIONS

Melting Point: Data unavailable

Boiling point: Data unavailable

## PURPOSE

Strengthener / binder for tobacco sheet; base material for cigarette paper.

## 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 | 1997 | - |

**FDA Status:**

| Section Number | Comments |
|---|---|
| - | - |

## HUMAN EXPOSURE

***Natural Occurrence:*** Cellulose is the most abundant biopolymer on earth. It is synthesised by all higher plants and a variety of other organisms. Cellulose as a raw material is reported as non-toxic, harmless, biodegradable and recyclable. It is used especially for producing fibres, films, water-soluble polymers and other chemicals [http://www.tut.fi/units/ms/teva/projects /cellulosefibre.html]. Natural cellulose is a white (polysaccharide) substance existing in both a microcrystalline form and a non-fibrous form, being constructed from glucose units linked together. The composition of cellulose on wood depends upon the type of wood, but is typically between 5-70 % with cotton and textile fibres of vegetable origin ranging fro m 65-95 % cellulose [HCN ,2002].

***Reported uses*** : C ellulose is used in food and beverage products as an emulsifier, stabiliser, anti-caking agent, and dispersing agent. It is also used in pharmaceuticals as a tablet and capsule diluent, and forms the basis for many materials used for chromatography, ion ex change resins, and in explosives manufacturing [JECFA, 1998]. The mean intake of dietary microcrystalline cellulose in the UK has been estimated as 0.65 g/person/day [JECFA, 1998].

## TOXICITY DATA

### *In Vivo* Toxicity Status

| Species | Test Type | Route | Reported Dosage |
|---|---|---|---|
| Rat | $LD_{50}$ | Oral | >3160mg/kg |
| Rat | $LD_{50}$ | Oral | >5000mg/kg |
| Rat | $LD_{50}$ | Intraperitoneal | >3169mg/kg |
| Rat | $LD_{50}$ | Inhalation | >5.3mg/litre |
| Rat | $LD_{50}$ | Dermal | >2000mg/kg |

[JECFA, 1998]

**Dermal Toxicity**

The application of 50 mg Cellulon ™, (a cellulo se fibre produced by the bacterial fermentation of employing a strain of *Acetobacter acetic* sub species *xylinium* most closely represents microcrystalline and powdered cellulose) in to the eyes of six rabbits was reported to be mildly irritating after 1 hou r but the redness had subsided 24 hours after application. A 500 mg sample of Cellulon™ applied to the shaved skin of six rabbits was reported to be well tolerated with no dermal effects [HCN, 2002].

**Reproductive and Developmental Toxicity**

Groups of 25 presumed pregnant Charles River Sprague-Dawley CD rats were administered 0 [control], 25,000 or 50,000 mg / kg Avicel [a proprietary microcrystalline cellulose] in the diet *ad libitum* on days 6 to 15 of gestation [equivalent to 2.2 and 4.6 g/kg bw/ day respectively]. The authors reported no evidence of reproductive toxicity, including teratogenicity, in any of the test animals. Under the conditions of the study, the maternal and foetal NOEL was > 50,000 mg/kg diet [equivalent to 4.6 g / kg bw / day] [JECFA, 1998].

**Inhalation Toxicity**

Groups of male Crl: CDBr rats were exposed to nose only to cellulose fibres for 6 hours/day 5days/week for 2 weeks, at target concentrations of 300 and 575 fibres per ml (with a median fibre length of 10-13 M). The lungs of the rat were then evaluated on Days 1, 10, and at 1 and 3 months after exposure by bronchoalveolar lavage. There was reported to be a moderate to slow clearance of cellulose fibres, with a transient pulmonary inflammatory response which was reported to have returned to control levels within 10 days post exposure [HCN, 2002].

Groups of Wistar rats were exposed via whole body inhalation to 0 (n = 3) or 1000 (n = 6) fibres/ml, 7 hours a day for 1, 3, 8 or 14 days of exposure during a 3 week period. The major ity of fibres were within the respirable size range with the mean concentration 73 mg/m$^3$. Inhalation was reported to be associated with an inflammatory response that peaked on the first day of exposure and declined with subsequent exposures. The *in vitro* production of the pro inflammatory cytokine tumour necrosis factor by lavaged alveolar macrophages had markedly declined by day 14 of exposure. The authors concluded that the inflammatory response in the lungs was less than that of crocidolite, and decreased over the 14 day exposure period [HCN, 2002].

It has been suggested that a large number of free radicals are generated by the burning of cellulose, and that radicals produced in the gas phase are metastable, but decompose in solution [Lachocki *et al.,* 1988]. The authors suggest that these free radicals could cause lung damage and question the role of free radicals in emphysema and carcinogenesis [Lachocki *et al.,* 1988].

Tatrai *et al.,* [1996] examined the pulmonary toxicity of cellulose. Sprague-Dawley-rats were given single intratracheal doses of 15 milligrams respirable cellulose and the lungs were examined morphologically after 6 and 12 months. The immune response to cellulose was also assessed at 1, 7, and 14

days after exposure, by examination of blood and bronchoalveolar lavage samples. Granulomatous inflammation was identified in the pulmonary interstitium of cellulose treated animals after 6 months. This was associated with damaged elastic fibres, decreased numbers of alveolar type-I pneumocytes and increased numbers of type-II pneumocytes. These changes were more pronounced after 12 months. Electron microscopy identified hypertrophic type-II cells, cytoplasmic lamellar inclusions in intermediate cells, thickened endothelial basement membranes, accumulation of collagen fibres in alveoli and capillary walls, and the presence of interstitial fibroblasts in alveolar walls. No alterations in serum immunoglobulin levels were seen. IgA was increased significantly in alveolar fluid 2 weeks after exposure. The authors conclude that these results underscore the importance of *in vivo* testing of cellulose as an asbestos substitute, and the urgency of developing a hygienic standard for cellulose use [Tatrai *et al.,* 1996]. In additional studies intratracheal administration of 15 mg of respirable germ free pine dust or cellulose were reported to cause identical changes inn the lungs of rats after one month, fibrosing alveobronchiolitis. As the severity of the histological findings between the two studies were not stated then, a direct comparison was not possible. A fibre free extract of the wood dust, however, was not reported to cause any histological changes of the lung [HCN, 2002].

A single Intratracheal dose of respirable cinnamon dust, cinnamon dust extract or cellulose were administered to rats that were sequentially examined 1 and 7 days, and 1 month after exposure. Histopathological examination revealed the formation of alveobronchiolitis at the end of the first and seventh days with fibrotic changes by the end of the fist month for both respirable cinnamon and cellulose. Ads the extract of cinnamon dust caused no histological changes the authors concluded that it was the cellulose content of the cinnamon dust that caused the histological changes [Tatrai *et al.,* 1995].

In a study conducted by Adamis *et al.,* (1997) male Sprague Dawley rats were intratracheally administered 15 mg of cellulose, quartz or saline. Rats were then serially sacrificed 1 - 30 days after a single exposure. Peritoneal macrophages were also incubated both in the presence and absence of cellulose. On the first day after exposure cellulose treatment resulted in an inflammatory response with leukocyte migration. One week after exposure there was reported to be oedema with cell infiltration in the alveoli and interstitium. Multinuclear foreign body cells were found to contain phagocytosed cellulose. At one month after exposure there was reported to be a widening of the alveolar septa, fibrosis of the alveoli and bronchi. Exposure to quartz reported to have lead to more extensive inflammatory response and marked fibrosis occurred. There was no lactate dehydrogenase (LDH) release from cellulose fibre exposed peritoneal macrophages. The authors concluded that cellulose dust was cytotoxic in the lungs when tested *in vivo*.

Intratracheal administration of 7.5 mg/kg (approximately 3 mg/g lung tissue) twice weekly for six weeks was reported caused pulmonary toxicity in hamsters (n = 4). The histological findings included significant numbers of granulomata and increased areas intra alveolar septa. The authors concluded

that the accumulation of particles and toxicity might be due to an overload of the lungs capacity to remove insoluble foreign material and the intrinsic toxicity of cellulose. The commi ttee concluded that it was unlikely that the threshold limit value (TLV) currently set for nuisance dusts of 5 mg/m $^3$ respirable fraction was likely to reach the intra tracheal level of 7.5 mg/kg, and that exposure by the intra tracheal route was more toxic than that via inhalation exposure. The committee also concluded that the current toxicological information was insufficient to recommend a health based exposure level [HCN, 2002].

**Other relevant studies**

Groups of five male weanling Sprague-D awley rats received 0 - 20 % cellulose in their diet over a period of 17 days. Absorption of magnesium and zinc were significantly lower in the higher dose groups [10 - 20 %]. Histopathology of the gastrointestinal tract revealed mitotic activity and an increase in n eutrophils in crypt epithelial cells, particularly of the duodenum and jejunum [JECFA, 1998].

Four rats were fed $^{14}$C-labelled microcrystalline cellulose at 10 or 20% of their diet. Faecal recoveries account for between 96 – 104% with no radioactivity appearing in the urine [JECFA 1998].

Rats, pigs and dogs have been used to study the persorption of microcrystalline cellulose. Animals were starved for 12 hours prior to administration of 0.5, 140 and 200 g of the test compound. Particles were found in the venous blood of all animals 1 - 2 hours after administration with the largest particle sizes being found in the blood of rats [JECFA 1998].

One human subject was fed 150g of microcry stalline cellulose daily for 15 days prior to receiving $^{14}$C-labelled cellulose. There was reported to be no excretion in either the respired air or urine, with all the activity (98.9 +/- 3 %) being found excreted in the faeces within 2 days [JECFA 1998].

Randomly bred rats of both sexes were divided into groups that received a control diet or a control diet plus 330 mg /kg microcrystalline cellulose for a period of 6 months. Six rats from each groups were killed, their organs examined, and tissues taken for histopathology. No effects of the treatment were observed [JECFA, 1998].

Groups of Crl:CD rats [20/ sex per group] were administered 0 [control] 25,000 or 50,000 mg/ kg bw Avicel [a proprietary microcrystalline cellulose] in the diet for 90 days. A few te st animals were reported to present with chromodacryorrhea [a flow of blood-stained tears] and chromorhinorrhea [a blood-stained nasal discharge], but the authors state that this was not considered to be biologically significant. The authors reported no ad verse effects for body weight, organ weights, or clinical chemistry for the test animals. Histopathological examination of 34 organs or tissues also provided no evidence of toxicity of microcrystalline cellulose. The authors noted that the NOEL exceeded 50,000 mg/kg diet [JECFA, 1998].

Avicel (which contained 85% microcrystalline cellulose and 15% calcium alginate) was administered at 0 or 45000 mg/kg in a high fibre diet in male Wistar rats, along with 1, 2-dimethyl hydrazine dihydrochloride (25 mg/kg subcutaneously once weekly for 16 weeks). There was reported to be a reduction in the numbers of animals bearing colon tumours and a significant reduction in the numbers of tumours/rat in the high fibre group. Tumours of the ear canal and small bowel there was no significant difference between any of the treatment groups [JECFA 1998].

Groups of Sprague Dawley rats (20 rats/dose/sex) were administered by oral gavage extra fine microcrystalline cellulose (particle size 6 m) at 0, 500, 2500 or 5000 mg/kg/day as a 25% suspension in water for 90 consecutive days. The only treatment related sign was reported to be pale faeces, however this was considered to be of no toxicological importance. There were no toxicological findings found, with no microcrystalline particles detected in any organ or tissue including gut associated lymphoid tissue, liver, lung, spleen and the brain. In the 5000 mg/kg/ group there was reported to be no histopathological findings reported in any the 36 tissues examined, with no macroscopic or microscopic changes due to microemboli or granulomatous inflammatory lesions [JECFA 1998].

Three groups of 50 male and 50 female rats received either: 30% ordinary cellulose, dry microcrystalline cellulose, or microcrystalline cellulose gel in their diet for 72 weeks. Male rats receiving the gel had higher liver and kidney weights compared with controls. Gross and histopathology showed some dystrophic calcification of renal tubules in females; all other organs were reported as unremarkable. Tumour incidence did not differ between the groups [JECFA, 1998].

Intravenous drug abuse of tablets has lead to the detection of microcrystalline deposits in various tissues of 21 fatality cases. In some cases there was reported to be an associated granulomatous lesion [JECFA 1998].

There was reported to be little data for epidemiological evidence of disease in workers although there are expected to be high levels of exposure in the work place. Epidemiological evidence although sparse, there is reported to be little evidence of disease even though there are high exposure levels in the work place. Exposures to hardwood associated dust has apparently been linked with the development of sinusoidal cancer, however soft woods were reported to be significantly less potent in their effects indicating that cellulose was not the causative agent. There exists a general lack of data on the pulmonary toxicity of inhaled cellulose. In summary the few *in vitro* and *in vivo* studies tat have been conducted suggest that respirable microcrystalline cellulose may be biopersistent in the lung and may produce pulmonary inflammation [Warheit *et al.,* 2001].

The addition of cellulose fibre at 28,400 ppm to reference cigarettes, used in a 90 day sub-chronic inhalation exposure in rats, led to a series of pathological changes to smoke exposure that were indistinguishable from those changes caused by the control cigarettes. This indicated that addition of cellulose fibre to a reference cigarette had no discernable effect upon the type or severity of

the treatment related pathological changes associated with tobacco smoke exposure [Baker *et al.,* 2004].

Le Leu *et al.,* (2009) compared control and cellulose based diets with a variety of high amylose maize starches (HAMS) diets in a 4-week study in Sprague-Dawley rats (n=12/group). The cellulose based diet showed similar outcomes to the control diet with respect to final body weight, caecal pH was comparable between cellulose diet and control diet , as was cell turnover and apoptotic index. Distal colon crypt atrophy was increased in control diet fed rats than in all other diets. Faecal output was found to be increased compared to control , with slightly increased caecal contents and slightly lower caecal weight compared to control . Levels of short chain fatty acids , a marker of fermentation, in the faeces and caecal contents were slightly decreased in the cellulose diet compared to the control diet [Le Leu *et al.,* 2009].

## BEHAVIOURAL DATA

No data identified

## *In Vitro* Toxicity Status

### Carcinogenicity and Mutagenicity

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".

JECFA (1998) reported that various cellulose preparations have been tested for genotoxicity in several different assay systems. Poor solubility/ pre-absorption of the test material were commonly quoted as a problem in carrying out the tests. Overall, JECFA (1998) reported that there was no evidence that microcrystalline cellulose is genotoxic. Results for genotoxicity assays are summarised below [JECFA, 1998]:

| Test system | Test cells | Concentration | Results |
|---|---|---|---|
| Reverse mutation | *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538 | 50 - 5000 µg/plate | Negative |
| Reverse mutation | *Escherichia coli* WP2*uvr*A | 10 - 5000 µg/plate | Negative |
| Forward mutation | Mouse lymphoma L5178Y cells, TK locus | 100 - 1000 µg/ml | Negative |
| UDS with confirmatory assay | Rat liver primary cell cultures | 10 - 1000 µg/ml | Negative |
| *In vivo* mammalian micronucleus assay | Bone marrow polychromatic erythrocytes of ICR mice | 5000 mg/kg bw - oral | Negative |
| *In vivo* mammalian | Bone marrow | 5000 mg/kg bw - | Negative |

| | | | |
|---|---|---|---|
| micronucleus assay | polychromatic erythrocytes of CD-1 [ICR] mice | oral | |

[JECFA, 1998].

Kuroda *et al*., (1985) reported on the mutagenicity of cellulose pyrolysates against a number of *Salmonella typhimurium* strains [Kuroda *et al.,* 1985]. The authors found that pyrolysed cellulose, 400 µg per plate, [at 500 - 800 C] led to the production of material [PAH's] that was mutagenic against TA97 in the presence of an S9 fraction. It had a positive mutagenic effect in strains TA98 and TA100 also, but there were less *His*$^{+}$ revertants [Kuroda *et al*., 1985].

Baker *et al.,* [2004]; examined the effects of the addition of 482 tobacco ingredients upon the biological activity and chemistry of mainstream smoke. The ingredients, essentially different groups of flavourings and casings, were added in differ ent combinations to reference cigarettes. The addition of cellulose fibre at 28,400 ppm was determined not to have affected the mutagenicity of the total particulate matter (TPM) of the smoke in either the Ames, *in vitro* micronucleus assay or the neutral r ed assay when compared with that of the control cigarettes [Baker *et al.,* 2004].

## REFERENCES


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