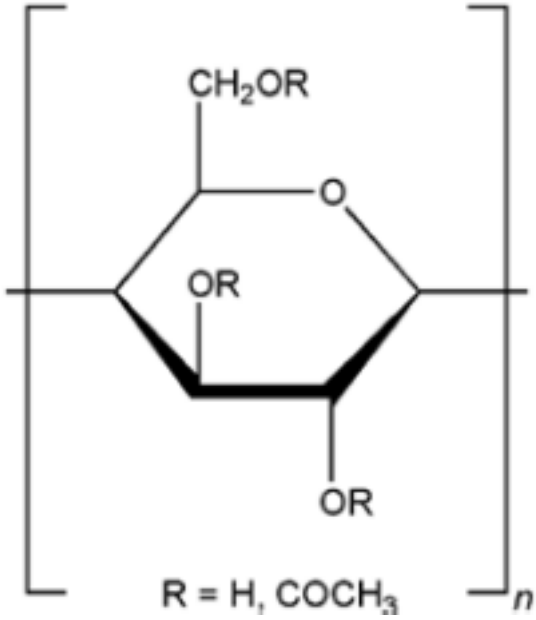
CELLULOSE ACETATE

SYNONYMS

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

Vladipor
t-Cellit

CHEMICAL STRUCTURE



CHEMICAL FORMULA

$(C_8H_{13}O_6)_n$

IDENTIFIER DETAILS

CAS Number	:	9004-35-7
CoE Number	:	-
FEMA	:	-
EINECS Number	:	-
E Number	:	-

SPECIFICATIONS

Melting Point: 260°C

Boiling point: Decomposes upon further heating.

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
-	-	-	-

FDA Status:[CFR21]

Section Number	Comments
175	**Indirect food additives: adhesives and components of coatings**
175.105	Adhesives.
175.230	Hot-melt strippable food coatings.
175.300	Resinous and polymeric coatings.
177	**Indirect food additives: polymers.**
177.1200	Cellophane.
182	**Substances generally recognized as safe.**
182.90	Substances migrating to food from paper and paperboard products.

HUMAN EXPOSURE

Natural Occurrence: Cellulose acetate was first prepared in 1865, and is the acetate ester of cellulose. Although the starting material cellulose occurs in nature cellulose acetate does not.

Reported Uses: Wide range of clothes , cigarette filters, ink reservoirs for fibre tip pens, disposable nappies, surgical products and playing cards.

TOXICITY DATA

Unless otherwise specified, the toxicological data that follows related to cellulose.

***In vivo* toxicity status**

Species	Test Type	Route	Reported Dosage
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]

Inhalation toxicity

In an experiment conducted by Agyei-Aye K et al., (2004) the release of cellulose acetate fibres, charcoal, and other particles from cigarettes with charcoal and activated charcoal/resin filters was investigated. For the first time in such studies, efforts were made to identify the particles that were eluted using other analytical techniques in addition to light microscopy. Other corrective measures were also implemented. During the studies it was found that trimming of larger filters to fit smaller filter housings introduced cellulose acetate-like particles from the fibres of the filter material. Special, custom made-to-fit filters were used instead. Tools such as forceps that were used to retrieve filters from their housings were also found to introduce fragments onto the filters. It is believed that introduction of such debris may have accounted for the very large number of cellulose acetate and charcoal particles that had been reported in the literature. Use of computerized particle-counting microscopes appeared to result in excessive number of particles. This could be because the filter or smoke pads used for such work do not have the flat and level surfaces ideal for computerized particle-counting microscopes. At the high magnifications that the pads were viewed for particles, constant focusing of the microscope would be essential. It was also found that determination of total particles by using extrapolation of particle count by grid population usually gave extremely high particle counts compared to the actual number of particles present. This could be because particle distributions during smoking are not uniform. Lastly, a less complex estimation of the thickness of the particles was adopted. This and the use of a simple mathematical conversion coupled with the Cox equation were utilized to assess the aerodynamic diameters of the particles. The authors concluded that their findings demonstrated that compared to numbers quoted in the literature, only a small amount of charcoal, cellulose acetate shards and other particles are released. It was also shown that those particles would have a low likelihood of reaching the lung, [Agyei-Aye *et al*., 2004].

Aerodynamic diameter is a major determinant of particle and fibre deposition and toxicity in the respiratory tract. To characterize cellulose acetate fibres released from the filter end of cigarettes puffed under conditions approximating smoking, Collazo *et al.,* (2002) designed multistage impactors to determine the aerodynamic diameters of large fibres with circumscribed diameters between 20 and 35 microm and aspect ratios ranging from subfibre ratios up to 40. This range of diameters encompasses all of the cellulose acetate fibre sizes that are commercially manufactured. When commercially available cigarettes with filters made from acetate fibres in this circumscribed diameter range were puffed directly into the impactor, on average 10 fibres/cigarette were released and their aerodynamic diameters were determined. In our studies, we found that the aerodynamic diameters of the cellulose acetate fibres were always greater than 23 microm. Using standard lung deposition models, we concluded that the fibres are nonrespirable with a very low probability of penetration to the distal lung. The authors conclude their findings demonstrate release of only a small number of these large fibres with an extremely low likelihood of reaching the distal lung indicate that these fibres are not a risk for human lung disease, [Collazo *et al*., 2002].

Dermal Toxicity

The application of 50 mg Cellulon ™, (a cellulose 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 hour 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 Av icel [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 tes t 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].

Other relevant studies

Groups of male Crl: CDBr rats were exposed to nose only to cellulose fibres for 6 h ours/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 w hole body inhalation to 0 (n=3) or 1000 (n=6) fibres/ml, 7 hours a day for 1,or 3,or 8,or 14 days of exposure during a 3-week period. The majority of fibres were within the respirable size range with the mean concentration 73.mg/m ^{3}. Inhalation was report ed 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 ar e 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 in 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, 7 days and 1 month after exposure. Histopathological examination revealed the formation of alveobronchiolitis at the end of the fist 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 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 committee 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 w as insufficient to recommend a health based exposure level [HCN, 2002].

In a study conducted by Thomas et al., (1991), c ellulose acetate was administered by way of a dietary admixture to Sprague-Dawley rats (20/sex/group) at dose levels of 0, 500, 2500 and 5000 mg/kg body weight/day for 94-96 days. Physical observations, body weight and food consumption measurements were made before testing and throughout the study. Ophthalmoscopic examinations were conducted on all animals before testing and just prior t o study termination. Haematology, clinical chemistry and urinalysis were performed at 1.5 and 3 months on 10 animals/sex/group. After 3 months of treatment the animals were killed, terminal body weights and organ weights were measured and ratios calculated . Histopathological examination of tissues from the control and high-dose groups was conducted. The authors concluded that the evaluation of physical observations, ophthalmology, body weight, food consumption, haematology, clinical chemistry, organ-to-body -weight ratios, gross pathology and histopathology revealed no evidence of an adverse effect related to treatment with cellulose acetate.

Lucas *et al.,* (2000) reported the results of an i nvestigation into the cause of conjunctivitis, hearing loss, diminis hed vision, and headaches in seven patients 7-24 h after h aemodialysis treatment. Eleven-year-old dialysis modules were identified as a common link between these patients. Degradation of the cellulose acetate (CA) material was identified as the cause of th is incident. Degradation products were characterized from retrieved CA dialysis membranes. A series of synthesized CA degradation products was tested in vitro to assess toxicity. Based on the toxicity of the material preparations to the cells, animal tests were performed on selected CA degradation extracts and compared to extracts from actual dialysis membranes. Rabbits were IV-injected with extracts from a 13-year-old dialyzer, synthesized model compounds, and compared to controls. Ophthamological evaluation of the rabbits showed eye injury (iritis/ciliary flush) when the animals were treated with the old dialyzer or synthesized model compounds. Isolation and characterization of a toxic fraction from both of these extracts strongly indicated that oxidative stress at some point in the storage or manufacture of CA dialyzers created degradation products that reproduced some of the patient symptoms identified at Hospital A.

Behavioural data

No data identified

In vitro Toxicity Status

Carcinogenicity and mutagenicity

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 micronucleus assay	Bone marrow polychromatic erythrocytes of CD-1 [ICR] mice	5000 mg / kg bw – oral	Negative

[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.,* [200 4] 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 different 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 red assay when compared with that of the control cigarettes [Baker *et al.,* 2004].

Other relevant studies

In a study conducted by Dang *et al.,* (1997) some commercial degradable plastics were tested in a cell culture screen including; a plasticized cellulose acetate, an aliphatic polye ster (Bionolle), polyhydroxybutyrate-co-hydroxyvalerate (Biopol), and polycaprolactone (TONE polymer). Cell culture medium with serum was used as extraction medium. Methods for the determination of morphology and viability of cells cultured in the extract were investigated. Phase-contrast light microscopy of cells, enhanced by neutral red staining, provides high-contrast images for qualitative evaluation of cell morphology and lysis. Compared to the determination of protein using the Bradford method and of neutral red uptake, the determination of dehydrogenase activity using 3-[4,5-dimethylthia-zol-2-yl]-2,5-diephenyl-tetrazolium bromide (MTT) is more sensitive and accurate. The relative MTT activity of cells cultured in fresh extracts indicate that TONE pol ymer (all shapes) and Bionolle (test bars and films) are comparable to materials currently used in the food industry (polyethylene terephthalate, atactic and isotactic polystyrene) with no toxic effects on cells.

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