Cellulose

(CAS Reg no: 9004-34-6)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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1 Introduction

The present document contains the assessment of the health hazard of cellulose by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by MA Maclaine Pont, M.Sc. (Wageningen University, Wageningen, the Netherlands).

Literature was retrieved from the data bases Toxline, Medline, and Chemical Abstracts, covering the periods 1981 to May 2000, 1966 to May 2000, and 1937 to March 2000, and using the following key words: (cellulose or 9004-34-6) and (occupational or skin or dermal or dust or inhal*). Data considered to be critical were evaluated by reviewing the original publications. The final literature search has been carried out in May 2000.

In July 2001, the President of the Health Council released a draft of the document for public review. The committee received no comments.

Occupational exposure to cellulose is expected in various jobs related to extracting cellulose from its original material and in the industries using the cellulose for further processing. However, in none of these jobs, the workers are exclusively exposed to cellulose.

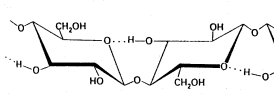
In 1972, the US Food and Drug Administration declared cellulose to be generally recognised as safe (GRAS), based upon a review of research between 1920 and 1972 (And92).

Cellulose from cotton can contain small amounts of waxes, pectin's, hemicellulose, metal salts like ferric chloride, and chemical defoliants (arsenic, quaternary ammonium compounds). In the processing of fibers into yarn, compounds are used like starch or a starch derivative, bleaching compounds, anti-statics, lubricants, several dyes, carriers to facilitate the dyeing, chemical binders to retain the dye on the surface, *etc.* (Bar75).

Cotton dust contains only 10-15% cellulose (Dom86). Paper dust and wood dust contain primarily compounds other than cellulose (Jäp87, Jag85).

In the production of cellulose triacetate, the exposure is mainly to dichloromethane (Lan90). In the production of viscose rayon, the exposure is mainly to carbon disulphide (Van91).

2 Identity

name	:	cellulose
synonyms	:	ß-amylose; alpha-cellulose; cupricellulose; hydroxycelllulose; pyrocellulose; sulphite cellulose
molecular formula	:	$(C_6H_{10}O_5)_n$
structural formula	:	
CAS reg no	:	9004-34-6

Data from How92.

Cellulose is a natural polysaccharide with the glucose units linked as in cellobiose. Cellulose is widely distributed in nature. Wood, depending on its type, contains about 50 to 70% cellulose. Cotton and textile fibers of vegetable origin, such as flax, hemp, and jute, contain 65 to 95% cellulose (ACG99).

Natural cellulose is a white substance existing in a microcrystalline form and as a nonfibrous form with a bulk density of 18 - 19 lb/ft^3 (288 - 305 kg/m^3). Technical cellulose refers to that portion of the plant cell wall derived exclusively from glucose in its physical and chemical properties. Unbleached sulphate cellulose, obtained from wood, contains 3 to 5% lignin and has a brown colour. Unbleached sulphite cellulose also obtained from wood, also contains 3 to 5 % lignin and has a very light brown colour (MoDo97).

Cellulon^{TM} fibre is a cellulose produced by a bacterial fermentation process employing a strain of *Acetobacter acetic* subsp *xylinum* and most closely resembles powdered and microcrystalline cellulose (Sch91).

3 Physical and chemical properties

molecular weight	:	300,000 to over 1,000,000
melting point	:	not found
boiling point	:	not applicable
flash point	:	-
vapour pressure	:	not applicable
solubility in water	:	practically insoluble
odour threshold	:	odourless
log $P_{octanol/water}$	:	not found
conversion factors (20^0C, 101.3 kPa)	:	not applicable

Data from ACG99, Har94.

4 Uses

Cellulose is primarily used for the preparation of textile fibers, *i.e.*, viscose (rayon), and for the production of paper and cardboard. For paper production, cellulose should contain at least 3% of lignin in order to maintain its strength (MoDo97). Cellulon™ fibre is used as a thickener and suspending agent of food (Sch91).

Derivatives of cellulose are used in a variety of applications:

- nitro-cellulose is used for the manufacturing of explosives, collodion, and lacquers.
- DEAE cellulose (diethylaminoethylcellulose) is used as ion exchange material in chromatography.
- cellulose acetates (partially acetylated) are used to prepare thermoplastic products: rubber and celluloid substitutes, photographic and cinema films, phonographic records, coating skins, insulating electric wires, *etc*.
- cellulose ethylhydroxyethylether is used as a laxative (Bud96).

5 Biotransformation and kinetics

The committee did not find data on the (toxico)kinetics of cellulose.

6 Effect and mechanism of action

Human data

Employment in cellulose plants was associated with a significantly increased incidence of gliomas, the predominant type of brain tumour among adults ($p<0.05$). The Cancer Environment Registry of Sweden was used, which links cancer incidence and employment data. At least 500 individuals were evaluated in the group of cellulose plant workers, and 45 cases were found (Standardised Incidence Ratio 1.6, compared with the general Swedish population). However, the authors explain the aetiology of the glioma as a result of exposure to acids, bleaches, finishing oils, and mercury compounds (McL87). There are no quantitative exposure data. The committee concludes that there is no proof that the gliomas are caused by exposure to cellulose.

In human studies with microcrystalline cellulose, doses up to 30 g/day were tolerated therapeutically as a bulk laxative (Mon82).

Animal data

Irritation and sensitisation

Instillation of 50 mg Cellulon™ into the eyes of 6 rabbits was mildly irritating 1 hour posttreatment. The redness subsided in all but one animal 24 hours after treatment. No irritation was noted in the cornea and iris (Sch91).

A dermal patch of 500 mg Cellulon™ applied for 4 hours on the shaved skin of 6 rabbits did not induce erythema, oedema, or other dermal effects (Sch91).

The committee did not find data on the potential sensitising properties of cellulose.

Acute toxicity

After a single oral dose in rats, the LD_{50} of Cellulon™ with sucrose (1 : 1) was greater than 2000 mg/kg (Sch91).

Inhalation exposure

A single inhalation exposure during 6 hours to respirable particles of cellulose had no effects in guinea pigs. The mean mass aerodynamic diameter (MMAD) was 2.9 - 3.0 µm, with a geometric standard deviation of 1.4 µm in both cases. The exposure concentration for each of the 4 animals ranged from 19.2 to 22.0 mg/m^3. The following parameters were measured or calculated prior to exposure, after 6 hours of exposure, and 18 hours postexposure: number of breaths per minute (f), tidal volume (V_T) and pressure changed during each breath (ΔP), V_T x f and flow resistive work per breath during inspiration and expiration. The lungs were not investigated histologically. A challenge with 10 % CO_2 before and after each exposure to cellulose did not influence the lung functions either (in all cases: $p>0.05$, compared with a control group). In a group of 4 guinea pigs exposed to cotton dust, all lung function parameters were affected ($p<0.05$) except V_T x f and flow resistive work per breath after 6 hours of exposure. The authors concluded that the different results after cotton and cellulose exposure rule out the possibility that the respiratory reactions were caused by mechanical properties of the dust (Ell84). The committee considers that this study cannot be used for the risk assessment since the exposure duration was too short.

Groups of male Crl:CDBR rats were exposed 'nose only' to cellulose fibres, 6 hours/day, 5 days/week, for 2 weeks. The target concentrations were 300 and 575 fibres/mL. The median length of the fibres was 10-13 µm. Following exposures, the lungs of rats were evaluated 3 and 10 days, as well as 1 and 3 months postexposure by bronchoalveolar lavage (BAL), and immediately after, as well as 10 days, 1, and 3 months for biopersistence/clearance studies. The inhalation exposure produced lung burdens in the range of $3x10^7$ fibres. Clearance of cellulose fibres was moderate to slow with mean values in the high dose group of $2.84x10^7$ reduced to $1.55x10^7$ after 3 months postexposure. The cellulose fibres produced a mild but transient pulmonary inflammatory response, which returned to control levels within 10 days postexposure (War98).

Groups of male Wistar rats were exposed 'whole body' to 0 (n=3) or 1000 fibres of cellulose / ml (n=6), 7 hours/day, for 1, 3, 8, and 14 days of actual exposure over a 3-week calendar period. An additional group of 6 exposed rats were maintained without further inhalation exposure, for a period of 28 days (after 14 days of actual exposure). The respirable fibres were well characterised: the size distribution was determined, as well as aerodynamic diameter and density. The bulk of the fibres was within the respirable range for rats. The concentration was 73 mg/m^3 (SE 1.8). Inhalation exposure induced an early

inflammatory response in rat lungs, as determined by bronchialveolar lavage, which peaked at day 1 following the start of inhalation and thereafter declined, despite a further 13 days of exposure. *In vitro* production of the pro-inflammatory cytokine tumour necrosis factor x (TNFα) by lavaged alveolar macrophages was markedly depressed by the end of the exposure period, compared to sham-exposed controls and this effect was still present in rats that had been allowed to recover for 28 days beyond the end of exposure. The authors concluded that the cellulose material studied was less inflammogenic than crocidolite and that the extent of the inflammatory response within the lungs appeared to reduce with continued exposure over a 14-day period (Cul00).

Intratracheal instillation

Intratracheal administration of cellulose dust into rats caused pulmonary toxicity. The size of the particles was not specified. A quantity of 15 mg instilled into the trachea of 10 male rats (body weight: 230-260 g), induced interstitial oedema, as well as signs of inflammation after 1 day. After one month the developing bronchioalveolitis was fibrous in character. Compared with quartz-treated rats the inflammatory processes were less explicit and less extensive. In the lungs of control rats, no histological changes or lymph nodes were observed. In the bronchoalveolar lavage, fluid protein, lactate dehydrogenase, acid phosphatase, phospholipid, and cell count were enhanced after days 1 and 3 ($p<0.01$) (Ada97).

Further observations on the animals were reported by Tatrai and coworkers. After 6 and 12 months, groups of 10 rats were investigated. A fibrosing alveobronchiolitis developed and with moderate progression by the end of the first year reached degree III according to Belt-King's system for classifying experimental fibrosis. Other rats were sacrificed one day, 7 days, and 2 weeks after a single intratracheal instillation of 15 mg cellulose and the IgG, IgA, and IgM levels were determined in blood and bronchoalveolar lavage (BAL). The IgA level was increased in BAL after 2 weeks ($p<0.05$). The other levels were not increased in serum and BAL at all time points. Secretory IgA is considered to be an important first line of defence against different agents and might be involved in the immunopathogenesis of fibrosing alveoli's (Tat96). The committee is aware of the severity of the bronchoalveolar effects but considers, at the same time, the route of administration as very burdensome.

A single intratracheal instillation of 15 mg respirable germ-free hardwood dust (pine) or cellulose caused identical histological changes in the lungs of rats after one month: fibrosing alveobronchiolitis. The authors did not indicate

whether the severity of the effects was comparable; therefore, the two treatments cannot be compared. A fibre-free extract from wood dust did not cause any histological changes in the lung (Tat95).

Intratracheal administration of 15 mg respirable paprika dust, free of fungi, or cellulose dust in rats caused alveobronchiolitis at the end of the first month and fibrotic changes at the end of the third month. The two treatments resulted in a comparable severity of the effects. A fibre-free extract from paprika dust resulted in no histological changes. The authors concluded that the effects caused by paprika dust can at least partly be ascribed to the cellulose present in the paprika (approximately 20%) (Tat92).

The committee concludes that the lung effects arising after exposure to germ-free wood dust or paprika dust, in combination with the absence of effects after exposure to fibre-free extracts, indicate that mainly the fibrous nature of the compounds is the cause of the effects.

Intratracheal instillation of cellulose dust into hamsters caused pulmonary toxicity. The MMAD of the particles was 4.8 µm. A quantity of 7.5 mg/kg bw (n=6) was instilled (approx. 3 mg/g lung), twice per week, for 6 weeks. Surviving animals (n=4) were killed 8 weeks after the last instillation. The animals had a decreased lung distensibility (n=4, $p<0.05$), normal surface-to-volume (S/V) ratio (n=6), and significant numbers of granulomata with patchy areas of thickened interalveolar septa (n=6, $p<0.05$). In the same study, groups of hamsters were exposed to cotton dust and endotoxins. Cellulose introduced the smallest change in lung distensibility, the largest number of granulomata and the smallest changes in surface density of the alveoli in the parenchyma (for all 3 compounds: $p<0.05$). The S/V ratio was decreased after exposure to cotton dust or endotoxins ($p<0.05$). The authors concluded that the accumulation of particles and toxicity may be due to an overload of the lung's capacity to remove insoluble foreign material as well as any intrinsic toxicity of cellulose. Such overload may occur from exposure to the level of respirable dust set by the ACGIH Nuisance Dust TLV (Mil90). The committee concludes that an overload of the lungs of hamsters with a respirable fraction of cellulose may have some effects on the alveoli. However, the effects are less severe than the effects of cotton dust or endotoxins. Further, the committee does not believe that exposure to levels at the TLV for nuisance dust (5 mg/m^3 respirable particles) leads to an intratracheal concentration of 7.5 mg/kg bw. Moreover, exposure by intratracheal instillation is more toxic than exposure by inhalation.

Oral administration

Anderson and co-workers reviewed the available data on long-term oral administration to laboratory animals, using purified cellulose. The chronic ingestion of purified cellulose over the entire lifespans in rats and mice does not result in any increase in spontaneous disease or neoplasia. Further, purified cellulose does not display promotional activity in the mammary gland, the colon, or the bladder of rats, and does not significantly alter the absorption or the metabolism of dietary compounds. At least two studies were considered valid by the authors in showing no adverse effects. However, the administered doses were not high: 3% and 5% of the diet. While these doses remove any confounding influence from caloric restriction, they are not the maximum doses desired to conclusively prove safety (And92).

Six African green monkeys (*Cercopithecus aethiops* spp vervets) were fed a diet containing 9.7% cellulose fibres for 3.5 years. They were killed and their intestines investigated. They served as a control group for 4 monkeys receiving a diet containing 9.7% psyllium husk. In the cellulose-fed group, mild damage was observed at villous tips of the duodenum, and there was a higher degree of necrosis in the lamina propria (results from scanning electron microscopy). No other effects were found (Pau87).

The feeding of rats with diets containing 0,5 or 10% Cellulon^{TM} for 13 weeks did not induce any toxic effects. The rats were compared with rats receiving diets with microcrystalline cellulose (positive control) and with rats receiving diets without cellulose (negative control). Also, the positive control group did not show any signs of toxicity compared with the negative control group (Sch91).

Mutagenicity and genotoxicity

Cellulon^{TM} fibre was negative or did not induce mutations in the:

- Ames assay, using *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538, with and without metabolic activation
- unscheduled DNA synthesis assay in rat hepatocytes
- chromosomal aberrations assay in Chinese hamster ovary (CHO) cells with and without metabolic activation
- HGPRT forward mutation assay (hypoxanthine-guanine phosphoribosyl transferase) in CHO cells with and without rat metabolic activation

(all studies: Sch91).

Reproduction toxicity

Anderson and co-workers reviewed the available data on reproduction toxicity of cellulose in laboratory animals. In 1972, the US Food and Drug Administration concluded that exogenous cellulose did not induce adverse reproductive effects, based on a 3-generation reproductive study in rats using purified cellulose at a 30% level in the diet. Also in subsequent studies, no adverse effects were found in reproduction or neonate development in rats and mice (And92).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for cellulose in the Netherlands is 2 mg/m^3, as inhalable particles as an 8-hour TWA.

Existing occupational exposure limits for cellulose in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

Cellulose is a rather inert material. In humans, bulk doses up to 30 g per day are used as a laxative (Mon82). In experimental animals, no effects have been found in rats and mice after lifetime dosing in the diet (And92). After 3.5 years of dosing via the diet, mild duodenal effects were observed in monkeys (Pau87). No reproduction toxicity was found after oral dosing in rats and mice (And92).

Cellulon^{TM}, a cellulose obtained by bacterial fermentation, was not a skin and eye irritant in rabbits (Sch91).

The only toxic effects induced by cellulose occurred after intratracheal instillation. The effects were localised in the lungs and not compound-specific, like an increase in protein particles, granolomas, bronchioalveolitis, or alveobronchiolitis. Probably, the fibrous nature of cellulose is the cause of the effects because fibre-free extracts from wood dust and paprika dust did not cause any histological changes in the lungs (Tat92, Tat95). However, the route of administration is not indicative for a possible target organ.

In a study with inhalation exposure of guinea pigs, no lung effects were observed after 6 hours of exposure to 19 - 22 mg/m^3 (Ell84). Higher concentrations were investigated in rats, where 575 x 10^6 fibers/m^3, as respirable particles inhaled for 2 weeks, only produced transient increases in pulmonary cell proliferative parameters (War98) and where 1000x10^6 fibres/m^3 (73 mg/m^3), intermittently inhaled for 3 weeks, also induced pulmonary inflammation in rats (Cul00). These studies cannot be used for the hazard assessment because the

exposure periods were too short, only one concentration was tested, and NOAELs were not obtained.

The committee considers the local irritant effect on lungs and trachea to be the critical effects.

The committee considers the toxicological data base on cellulose too poor to justify recommendation of a health-based occupational exposure limit.

The committee concludes that there is insufficient information to comment on the level of the present MAC-value.

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Annex

Occupational exposure limits for cellulose in various countries.

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	lit ref[b]
	ppm	mg/m^3				
the Netherlands						
- Ministry of Social Affairs and Employment	-	2[c]	8 h	administrative		SZW01
Germany						
- AGS	-	-				TRG00
- DFG MAK-Kommission	-	-				DFG01
Great Britain						
- HSE	-	10[c]	8 h	OES		HSE01
	-	20[c]	15 min			
	-	4[d]	8 h	OES		
Sweden	-	-				Arb00b
Denmark	-	-				Arb00a
USA						
- ACGIH	-	10	8 h	TLV		ACG01
- OSHA	-	15[e]	8 h	PEL		ACG00
	-	5[d]	8 h	PEL		
- NIOSH	-	10[e]	10 h	REL		ACG00
		5[d]	10 h	REL		
European Union						
- SCOEL	-	-				CEC00

[a] S = skin notation, which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation

[b] Reference to the most recent official publication of occupational exposure limits

[c] (Total) inhalable dust

[d] Respirable fraction

[e] Total dust