Toxicological profile for

Cellulose

This ingredient has been assessed to determine potential human health effects for the consumer. It was considered not to increase the inherent toxicity of the product and thus is acceptable under conditions of intended use.

1. Name of substance and physico-chemical properties

1.1. IUPAC systematic name

No data available to us at this time.

1.2. Synonyms

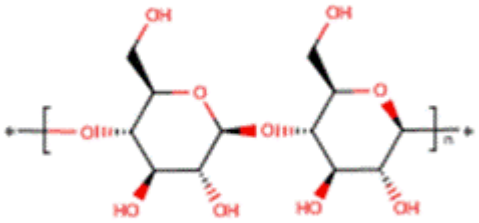
Abicel; Alpha Cel PB 25; Arbocel; Arbocel BC 200; Arbocell B 600/30; Avicel; Avicel 101; Avicel 102; Avicel CL 611; Avicel PH; Avicel PH 101; Avicel PH 105; CCRIS 6600; CEPO; CEPO S 20; CEPO S 40; Cellex MX; Cellulose; Cellulose 248; Cellulose crystalline; Cellulose, microcrystalline; Celphere CP-305; Cellulose regenerated; Celufi; Cepo CFM; Chromedia CC 31; Chromedia CF 11; CP-305; Crystalline cellulose; Cupricellulose; Dispersible cellulose; EINECS 232-674-9; Elcema F 150; Elcema G 250; Elcema P 050; Elcema P 100; Fresenius D 6; Heweten 10; Hydroxycellulose; Kingcot; Klucel; LA 01; MN-Cellulose; Microcrystalline cellulose; Onozuka P 500; Pyrocellulose; Rayophane; Rayweb Q; Rexcel; Sentry aq mardel clout; Sigmacell; Solka-fil; Solka-floc; Solka-floc BW; Solka-floc BW 100; Solka-floc BW 20; Solka-floc BW 200; Solka-floc BW 2030; Spartose OM-22; Sulfite cellulose; Tomofan; Tunicin; UNII-I355QGZ19A; UNII-OP1R32D61U; UNII-SMD1X3XO9M; Whatman CC-31; alpha-Cellulose; beta-Amylose; Rayon; Rayon flock; Wood pulp, bleached; Avicel RC/CL; alpha-Cellulose; UNII-C8DF2GF8L2; Cellulose, respirable fraction; Cellulose, total dust (ChemIDplus)

1.3. Molecular formula

(C6 H10 O5) x; unspecified (ChemIDplus)

1.4. Structural Formula

(ChemIDplus)



1.5. Molecular weight (g/mol)

160,000-560,000; 324.28 (ChemIDplus); approximately 50,000–2,500,000 (EFSA, 2018)

1.6. CAS registration number

9004-34-6

1.7. Properties

1.7.1. Melting point

(°C): 500

1.7.2. Boiling point

(°C): Decomposes

1.7.3. Solubility

No data available to us at this time.

1.7.4. pKa

pH 5.0 (100 g/l, H_2O, 20°C)

1.7.5. Flashpoint

(°C): about 260 (IUCLID, 2000)

1.7.6. Flammability limits (vol/vol%)

No data available to us at this time.

1.7.7. (Auto)ignition temperature

(°C): 232 (IUCLID, 2000)

1.7.8. Decomposition temperature

(°C): Not available.

1.7.9. Stability

Stable at normal temperatures and pressure.

1.7.10. Vapor pressure

Not applicable.

1.7.11. log Kow

Not available.

2. General information

2.1. Exposure

“The substance is used as a raw material in the manufacture of a number [of] cellulose derivatives” As taken from IUCLID, 2000.

Cellulose and microcrystalline cellulose (both CAS RN 9004-34-6) are used as bulking, absorbent, opacifying and viscosity controlling agents in cosmetics in the EU. In addition, microcrystalline cellulose is also used as an anticaking, emulsion stabilising and stabilising

agent. As taken from CosIng (Cosmetic substances and ingredients database). Available at https://ec.europa.eu/growth/tools-databases/cosing/, accessed October 2019.

Cellulose, microcrystalline (CAS RN 9004-34-6) is listed as an ingredient (at given concentrations, where specified) in auto (at up to 10%), commercial/institutional (at up to 10%), home maintenance (at up to 15%), inside the home (at 10-100%), landscape/yard (at >1-70%), personal care (at 0.5-<10%), pesticide (at 40-70%) and pet care products by the US Department of Health and Human Services (2019).

As a raw material, it forms the basis for many derivatives used in chromatography, ion exchange materials, explosives manufacturing, and pharmaceutical preparations (ChemIDplus).

“The combined exposure to celluloses (E 460–466, E 468 and E 469) at 95th percentile of the refined (brand-loyal) exposure assessment for the general population was up to 506 mg/kg bw per day.”

“The Panel considered an indicative total exposure of around 660–900 mg/kg bw per day for microcrystalline, powdered and modified celluloses.”

As taken from EFSA, 2018

2.2. Combustion products

Cellulose has been pyrolysed many different ways. The pyrolysis products were phenol; pyrogallol; m-cresol; o-cresol; p-cresol; formaldehyde; acetaldehyde; propionaldehyde; n-butyraldehyde; 2-furaldehyde; 5-hydroxymethylfuraldehyde; 5-methyl-2-furaldehyde; acetone; methyl ethyl ketone; acrolein; 2-buten-3-one; 3-hydroxy-2-methylpyran-4-one; 3-methyl-2, 4-(3H, 5H)-furandione; 1,3-cyclopentanedione; glucopyranose; picene; benzo(a)pyrene; fluoranthrene; anthracene; 4, 5-methylenphenanthrene; phenanthrenequinone; anthraquinone; pyrenequinone; furfural; 5-hydroxymethylfurfural; furancarboxylic acid methyl ester; propionic acid methyl ester; 3-methylfuran; methanol; 2-furanmethanol; glyoxal; formic acid; acetic acid; lactic acid; carbon monoxide; carbon dioxide; water; levoglucosan (Bell *et al* 1966; Schlotzhauer *et al* 1967 & 1985; Sakuma *et al* 1981; Kroller 1964a; Lewin & Basch 1978).

Cellulose Pyrolysate contained more benzopyrene than tobacco pyrolysate (Gilbert & Lindsay, 1957; Robb *et al* 1966).

Pyrolysis of cellulose yields a greater percentage of low molecular weight ketones and aldehydes, such as acetaldehyde and hydroxyacetaldehyde, relative to glucose, fructose and sucrose (Sanders et al. 2002).

This ingredient was investigated in a pyrolysis study. Results are given in JTI Study Report (s).

Compound	Two stage heating		One stage heating	
	Abundance	Area%	Abundance	Area%
acetone	17205988	1.06	8355698	0.57
acetic acid	256330301	1.58	23513104	1.60
acetol	34103603	2.10	24177932	1.65
2-cyclopenten-1-one + unknown	34670406	2.14	22937462	1.56
furfural	47125884	2.90	56584048	3.86

1,2-cyclopentanedione	18899160	1.16	12472713	0.85
3-methyl-2,5-furandione + unknown	26846932	1.65	23115994	1.58
2H-pyran-2,6(3H)-dione	29606121	1.82	21465379	1.46
2-furancarboxylic acid	23045299	1.42	20692827	1.41
3,5-dihydroxy-2-methyl-4H-pyran-4-one	18322628	1.13	20068994	1.37
unknown	42470578	2.62	37686848	2.57
1,4:3,6-dianhydro-alpha-D-glucopyranose	23637096	1.46	20544754	1.40
5-hydroxymethylfurfural	78400335	4.83	81445343	5.55
unknown	17834203	1.10	10476614	0.71
unknown	17213131	1.06	12222776	0.83
unknown	57099159	3.52	44673662	3.05
levoglucosan	561411098	34.57	625527613	42.64
1,6-anhydro-beta-D-glucofuranose	40779397	2.51	34278165	2.34
Total ion chromatogram	**1624677171**	**100**	**1464878846**	**100**

“A rapid, semi-micropyrolysis technique was developed and applied to materials representative of tobacco cell-wall constituents and sucrose. Glass capillary gas chromatography - mass spectrometry was used to separate and identify the major semi-volatile pyrolyzate components. Cellulose and dextrin produced a pattern of furan and cyclic ketones of potential importance to flavour and aroma of tobacco smoke. Sucrose pyrolysis resulted in the formation of substantial amounts of 2-furaldehyde and lesser quantities of substituted furans. The cell-wall biopolymer lignin was a source of phenols, but contributed little to the compounds produced in the thermal breakdown of carbohydrates.” As taken from Schlotzhauer WS et al. 1985. Beiträge zur Tabakforschung 13(2), 74-80. Available at: http://www.degruyter.com/view/j/cttr.1985.13.issue-2/cttr-2013-0558/cttr-2013-0558.xml?rskey=fIuZed&result=17

2.3. Ingredient(s) from which it originates

“It is the chief constituent of plant fibers, cotton being the purest natural form of the substance.”

As taken from ChemIDplus.

Cellulose (CAS RN not given) is found in stem bark from ambrette, dry stems of genet, kola nut, tragacanth (1-4%) and luffa sponge.

As taken from Khan and Abourashed, 2010

“Microcrystalline cellulose is purified, partially depolymerised cellulose prepared by treating α-cellulose, obtained as a pulp from strains of fibrous plant material, while powdered cellulose is purified, mechanically disintegrated cellulose prepared by processing α-cellulose.

As taken from EFSA, 2018

3. Status in legislation and other official guidance

Evaluations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA):

Amylose and Amylopectin

Synonyms:	Amylose and amylopectin
CAS number:	9004-34-6 (CELLULOSE, BETA-AMYLOSE)
Functional Class:	Food Additives THICKENER
Evaluation year:	1982
ADI:	NOT SPECIFIED
Meeting:	26
Specs Code:	O
Report:	TRS 683-JECFA 26/29
Tox Monograph:	FAS 5/NMRS 53A-JECFA 17/340 (1973)
Specification:	NOT PREPARED
Previous Years:	1973, NMRS 53/TRS 539-JECFA 17/37, NOT PREPARED, FAS 5/NMRS 53A-JECFA 17/340. ADI NOT LIMITED. NL. O 1970, NMRS 46/TRS 445-JECFA 13/13, NOT PREPARED, FAS 70.36/NMRS 46A-JECFA 13/60. ADI NOT LIMITED (THESE NATIVE STARCHES SHOULD BE REGARDED AS FOOD RATHER THAN FOOD ADDITIVES). NL. O

MICROCRYSTALLINE CELLULOSE:

Synonyms:	CELLULOSE GEL
Chemical Names:	CELLULOSE
CAS number:	9004-34-6
INS:	460
Functional Class:	Food Additives: ANTICAKING_AGENT EMULSIFIER STABILIZER
Evaluation year:	1997
ADI:	NOT SPECIFIED
Meeting:	49
Specs Code:	R
Report:	TRS 884-JECFA 49/14
Tox Monograph:	FAS 40-JECFA 49/55
Specification:	COMPENDIUM ADDENDUM 8/FNP 52 Add.8/65 (2000). R; FAO JECFA Monographs 1 vol.2/355
Previous Years:	1998, COMPENDIUM ADDENDUM 6/FNP 52 Add.6/87. R 1997, COMPENDIUM ADDENDUM 5/FNP 52 Add.5/71. R 1996, COMPENDIUM ADDENDUM 4/FNP 52 Add.4/107. R 1995, COMPENDIUM ADDENDUM 3/FNP 52 Add.3/97. R 1975, NMRS 55/TRS 576-JECFA 19/15, SPECIFICATIONS CONTINUED, F

POWDERED CELLULOSE:

Chemical Names:	CELLULOSE; LINEAR POLYMER OF 1:4 LINKED GLUCOSE RESIDUES
CAS number:	9004-34-6
INS:	460ii

Functional Class:	Food Additives ANTICAKING_AGENT EMULSIFIER TEXTURIZER THICKENER
Evaluation year:	1976
ADI:	NOT SPECIFIED
Meeting:	20
Specs Code:	N
Report:	FNS 1/TRS 599-JECFA 20/12
Tox Monograph:	FAS 8/NMRS 55A-JECFA 19/47 (1975,MICROCRYSTALLINE CELLULOSE)
Specification:	COMPENDIUM ADDENDUM 9/FNP 52 Add.9/192 (METALS LIMITS) (2001). R; FAO JECFA Monographs 1 vol.3/163
Previous Years:	1976, FAS 11/FNS 1B-JECFA 20/77. N; COMPENDIUM/1199 1973, NMRS 53/TRS 539-JECFA 17/21, FNP 4-JECFA 17/85, FAS 5/NMRS 53A-JECFA 17/297 (MICROCRYSTALLINE CELLULOSE). ADI NOT LIMITED. NL. N

As taken from JECFA, 2019 available at http://apps.who.int/food-additives-contaminants-jecfa-database/search.aspx

The (former) EU Scientific Committee on Food placed cellulose in List 0, as a compound that can be used in food-contact materials without the need for establishing an ADI figure (Commission, 2002).

“Cellulose is authorised as additive for plastic materials and articles in contact with foods, with no specific restriction (FCM Substance No 553).” As taken from EFSA, 2014.

High production volume (HPV) chemical; in excess of 1 million pounds produced in US annually (Scorecard).

Cellulose is included on the FDA’s list of Indirect Additives used in Food Contact Substances and covered under 21 CFR 179.45 (IRRADIATION IN THE PRODUCTION, PROCESSING AND HANDLING OF FOOD. PACKAGING MATERIALS FOR IRRADIATED FOODS. Packaging materials for use during the irradiation of prepackaged foods). As taken from FDA (2019a,b).

The short-term exposure limit (15 min reference period) for cellulose inhalable dust is 20 mg/m^3.

The long-term exposure limit (8-hour TWA reference period) for cellulose inhalable dust is 10 mg/m^3 and respirable is 4 mg/m^3.

As taken from HSE, 2018.

ACGIH TLV 8-hr TWA: 10 mg/m^3

OSHA PELs TWA: 15 mg/m^3 (total dust); 5 mg/m^3 (respirable fraction)

NIOSH RELs 10-hr TWA: 10 mg/m^3 (total dust); 5 mg/m^3 (respirable fraction)

As taken from ACGIH, 2019a.

OCCUPATIONAL EXPOSURE LIMITS:

OEL-BELGIUM: TWA 10 mg/m3, MAR2002

OEL-FRANCE: VME 10 mg/m3, FEB2006

OEL-KOREA: TWA 10 mg/m3, 2006

OEL-MEXICO: TWA 10 mg/m3;STEL 20 mg/m3, 2004

OEL-THE NETHERLANDS: MAC-TGG 2 mg/m3, 2003

OEL-NEW ZEALAND: TWA 10 mg/m3 (inspirable dust), JAN2002

OEL-RUSSIA: STEL 10 mg/m3, JUN2003

OEL-SWITZERLAND: MAK-W 3 mg/m3, resp, JAN2011

OEL-UNITED KINGDOM: TWA 10 mg/m3;STEL 20 mg/m3 (inhal. dust), OCT2007

OEL-UNITED KINGDOM: TWA 4 mg/m3 (resp. dust), OCT2007

OEL IN ARGENTINA, BULGARIA, COLOMBIA, JORDAN check ACGIH TLV;

OEL IN SINGAPORE, VIETNAM check ACGIH TLV

As taken from RTECS, 2017.

US Army Military exposure guidelines (MEGs) for Short-Term exposures to chemicals in ambient air:

1 hour Critical Air MEG 5.0E+02 mg/m^3

1 hour Marginal Air MEG 5.0E+02 mg/m^3

1 hr Negligible air MEG 3.0E+01 mg/m^3

14 day Negligible air MEG 3.4E+00 mg/m^3

8 hour Negligible air MEG 1.0E+01 mg/m^3

Potential health effects irrit eyes , irrit muc memb , irrit skin

US Army Military exposure guidelines (MEGs) for Long-Term exposures to chemicals in ambient air:

Component Name Value

1 year Negligible air MEG 3.40E+00 mg/m^3

Potential health effects irrit eyes , irrit muc memb , irrit skin

As taken from US EPA ACToR database, 2015.

	Limit value - Eight hours		Limit value - Short term	
	ppm	mg/m^3	ppm	mg/m^3

Australia		10 (1)		
Belgium		10		
Canada - Ontario		10		
Canada - Québec		10		
France		10 inhalable aerosol		
Ireland		10 (1)		20 (1)(3)
		4 (2)		
Latvia		2		
New Zealand		10 (1)		
People's Republic of China		10		
Singapore		10		
South Korea		10		
Spain		10 inhalable aerosol		
Switzerland		3 respirable aerosol		
USA - NIOSH		10 (1)		
		5 (2)		
USA - OSHA		15 total dust		
		5 respirable dust		
United Kingdom		10 inhalable aerosol		20 inhalable aerosol
		4 respirable aerosol		
	Remarks			
Australia	(1) This value is for inhalable dust containing no asbestos an <1 % crystalline silica.			
Ireland	(1) Inhalable fraction (2) Respirable fraction (3) 15 minutes reference period			
New Zealand	(1) The value for inhalable dust containing no asbestos and less than 1% free silica.			
USA - NIOSH	(1) Total dust (2) Respirable aerosol			

As taken from GESTIS, 2019, available at https://limitvalue.ifa.dguv.de/

Listed as a fragrance ingredient by the International Fragrance Association (IFRA, 2016).

Cellulose (CAS RN 9004-34-6) is pre-registered under REACH (“envisaged registration deadline 30 November 2010”) (ECHA, 2018).

Cellulose (CAS RN 9004-34-6) is not classified for packaging and labelling under Regulation (EC) No. 1272/2008 (ECHA, 2019).

Cellulose (CAS RN 9004-34-6) is listed in the US EPA InertFinder Database (2019) as approved for food and non-food use pesticide products. For food use, it is regulated under 40 CFR Part 180.950 (Tolerances and Exemptions for Pesticide Chemical Residues in Food. Tolerance exemptions for minimal risk active and inert ingredients) (US EPA, 2019a).

The EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing aids concluded that the use of cellulose in oxygen absorber/carbon dioxide emitter systems in sachets that prevent the physical release of their contents into the food does not raise a safety concern (EFSA, 2014).

Cellulose (CAS RN 9004-34-6) is included on the list of Safer Chemical Ingredients (US EPA, 2019b).

Cellulose (CAS RN 9004-34-6) is listed in the US EPA Toxic Substances Control Act (TSCA) inventory, and also in the US EPA 2012 CDR and 2016 CDR Full Exempt lists (Chemical Data Reporting Rule). The Chemical Data Reporting (CDR) Rule requires

companies that manufacture (including import) certain chemicals at certain volumes in the U.S. to report to EPA every four years through its CDR.

The TSCA inventory, and 2012 CDR and 2016 CDR Full Exempt lists are available at https://iaspub.epa.gov/sor_internet/registry/substreg/searchandretrieve/searchbylist/search.do

“Microcrystalline cellulose (E 460(i)) and powdered cellulose (E 460(ii)) have been previously evaluated by the Scientific Committee on Food (SCF), the most recent evaluation dating in 1999. In 1999, the SCF assessed additional toxicological data and confirmed the ‘ADI not specified’, established in 1978. As a matter of precaution, the Committee repeated the advice given in 1995, according to which, the particle size should not be lower than 5 lm with a tolerance of 10% by the number of particles.”

“The 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 (E 460(i); E 460(ii); E 461–466; E 468 and E 469).”

“The Panel recommended that the European Commission considers lowering the maximum limits for the toxic elements arsenic, lead, mercury and cadmium present as impurities in the EU specifications for unmodified and modified celluloses re-evaluated in the present opinion (E 460(i), E 460(ii), E 461, E 462, E 463, E 464, E 465, E 466, E 468 and E 469) should be revised to ensure that these food additives will not be a significant source of exposure to these toxic elements in food, in particular for infants and children.”

As taken from EFSA, 2018

Permissible exposure limit (PEL) for Cellulose (paper fiber) (CAS RN 9004-34-6): see Particulates not otherwise regulated.

Permissible exposure limit (PEL) for Particulates not otherwise regulated[(f)]
Total dust: 10 mg/m^3
Respirable fraction[(n)]: 5 mg/m^3

(f) Milligrams of substance per cubic meter of air at 25°C and 760mm Hg pressure.

(n) The concentration and percentage of the particulate used for this limit are determined from the fraction passing a size selector with the following characteristics:

Aerodynamic Diameter in Micrometers (unit density sphere)	*Percent Passing Selector*
0	100
1	97
2	91
3	74
4	50
5	30
6	17
7	9
8	5
10	1

As taken from Cal/OSHA, available at https://www.dir.ca.gov/title8/5155table_ac1.html#_blank

Cellulose (CAS RN 9004-34-6) is listed by the US EPA Office of Pesticide Programs (2019) and was first registered on 27 August 2003.

Cellulose (E460) is authorised for use as a food additive in the EU under legislation (EU) nos 1129/2011 and, as a Group I additive, also under 438/2013, 2015/0647 and 2018/1497. Microcrystalline cellulose, cellulose gel (E460(i)) and powdered cellulose (E460(ii)) are also authorised under legislation (EU) nos 1124/2013 and 1129/2011, respectively (European Commission, 2015, 2016 & 2019).

Cellulose (CAS RN 9004-34-6) is included on the New Zealand Inventory of Chemicals and may be used as a single component chemical under appropriate group standard (NZ EPA, 2006).

Cellulose (CAS RN 9004-34-6) has been “identified as low concern to human health by application of expert validated rules” and is “not considered to pose an unreasonable risk to the health of workers and public health on the basis of the Tier I IMAP assessment” (NICNAS, 2018).

Microcrystalline cellulose and powdered cellulose (both CAS 9004-34-6) are included on the US FDA’s list of inactive ingredients for approved drug products. They are permitted for use as ingredients in various products, at the following maximum potencies per unit dose:

Inactive Ingredient	**Route**	**Dosage Form**	**CAS Number**	**UNII**	**Maximum Potency per unit dose**
MICROCRYSTALLINE CELLULOSE	BUCCAL	TABLET, EXTENDED RELEASE	9004346	PNR0YF693Y	18.04mg
MICROCRYSTALLINE CELLULOSE	INTRAVITREAL	IMPLANT	9004346	PNR0YF693Y	1.66mg
MICROCRYSTALLINE CELLULOSE	NASAL	SPRAY, METERED	9004346	PNR0YF693Y	0.02mg/mg
MICROCRYSTALLINE CELLULOSE	ORAL	CAPSULE	9004346	PNR0YF693Y	361.52mg
MICROCRYSTALLINE CELLULOSE	ORAL	CAPSULE, COATED PELLETS	9004346	PNR0YF693Y	57.03mg
MICROCRYSTALLINE CELLULOSE	ORAL	CAPSULE, DELAYED RELEASE	9004346	PNR0YF693Y	60mg

MICROCRYSTALLINE CELLULOSE	ORAL	CAPSULE, EXTENDED RELEASE	9004346	PNR0YF693Y	306.8mg
MICROCRYSTALLINE CELLULOSE	ORAL	CAPSULE, GELATIN COATED	9004346	PNR0YF693Y	60.15mg
MICROCRYSTALLINE CELLULOSE	ORAL	GRANULE	9004346	PNR0YF693Y	81.6mg
MICROCRYSTALLINE CELLULOSE	ORAL	GRANULE, FOR SUSPENSION	9004346	PNR0YF693Y	0.13mg/mg
MICROCRYSTALLINE CELLULOSE	ORAL	PELLET	9004346	PNR0YF693Y	31.36mg
MICROCRYSTALLINE CELLULOSE	ORAL	POWDER, FOR SOLUTION	9004346	PNR0YF693Y	0.75mg
MICROCRYSTALLINE CELLULOSE	ORAL	POWDER, FOR SUSPENSION	9004346	PNR0YF693Y	550mg
MICROCRYSTALLINE CELLULOSE	ORAL	SUSPENSION	9004346	PNR0YF693Y	20mg/1ml
MICROCRYSTALLINE CELLULOSE	ORAL	SUSPENSION, EXTENDED RELEASE	9004346	PNR0YF693Y	0.13mg/mg
MICROCRYSTALLINE CELLULOSE	ORAL	TABLET	9004346	PNR0YF693Y	1553mg
MICROCRYSTALLINE CELLULOSE	ORAL	TABLET, CHEWABLE	9004346	PNR0YF693Y	639mg
MICROCRYSTALLINE CELLULOSE	ORAL	TABLET, CHEWABLE, EXTENDED RELEASE	9004346	PNR0YF693Y	96mg
MICROCRYSTALLINE CELLULOSE	ORAL	TABLET, COATED	9004346	PNR0YF693Y	356mg

MICROCRYSTALLINE CELLULOSE	ORAL	TABLET, COATED PARTICLES	9004346	PNR0YF693Y	391mg
MICROCRYSTALLINE CELLULOSE	ORAL	TABLET, DELAYED RELEASE	9004346	PNR0YF693Y	736.83mg
MICROCRYSTALLINE CELLULOSE	ORAL	TABLET, DELAYED RELEASE PARTICLES	9004346	PNR0YF693Y	289.9mg
MICROCRYSTALLINE CELLULOSE	ORAL	TABLET, EXTENDED RELEASE	9004346	PNR0YF693Y	723.12mg
MICROCRYSTALLINE CELLULOSE	ORAL	TABLET, FILM COATED	9004346	PNR0YF693Y	665.36mg
MICROCRYSTALLINE CELLULOSE	ORAL	TABLET, FILM COATED, EXTENDED RELEASE	9004346	PNR0YF693Y	328.36mg
MICROCRYSTALLINE CELLULOSE	ORAL	TABLET, FOR SUSPENSION	9004346	PNR0YF693Y	340mg
MICROCRYSTALLINE CELLULOSE	ORAL	TABLET, MULTILAYER, EXTENDED RELEASE	9004346	PNR0YF693Y	34mg
MICROCRYSTALLINE CELLULOSE	ORAL	TABLET, ORALLY DISINTEGRATING	9004346	PNR0YF693Y	415.92mg
MICROCRYSTALLINE CELLULOSE	ORAL	TABLET, ORALLY DISINTEGRATING, DELAYED RELEASE	9004346	PNR0YF693Y	262.65mg
MICROCRYSTALLINE CELLULOSE	ORAL	TABLET, SUGAR COATED	9004346	PNR0YF693Y	4.64mg
MICROCRYSTALLINE CELLULOSE	ORAL	TROCHE	9004346	PNR0YF693Y	60mg

MICROCRYSTALLINE CELLULOSE	SUBLINGUAL	TABLET	9004346	PNR0YF693Y	43.2mg
MICROCRYSTALLINE CELLULOSE	VAGINAL	TABLET	9004346	PNR0YF693Y	390mg
POWDERED CELLULOSE	BUCCAL	TABLET	9004346	SMD1X3XO9M	4.5mg
POWDERED CELLULOSE	DENTAL	PASTE, DENTIFRICE	9004346	SMD1X3XO9M	NA
POWDERED CELLULOSE	EXTRACORPOREAL	DISC	9004346	SMD1X3XO9M	NA
POWDERED CELLULOSE	ORAL	CAPSULE	9004346	SMD1X3XO9M	405mg
POWDERED CELLULOSE	ORAL	CAPSULE, EXTENDED RELEASE	9004346	SMD1X3XO9M	8.5mg
POWDERED CELLULOSE	ORAL	DROPS	9004346	SMD1X3XO9M	NA
POWDERED CELLULOSE	ORAL	LIQUID	9004346	SMD1X3XO9M	NA
POWDERED CELLULOSE	ORAL	POWDER, FOR SUSPENSION	9004346	SMD1X3XO9M	NA
POWDERED CELLULOSE	ORAL	SUSPENSION	9004346	SMD1X3XO9M	100mg/5ml
POWDERED CELLULOSE	ORAL	TABLET	9004346	SMD1X3XO9M	560mg
POWDERED CELLULOSE	ORAL	TABLET, CHEWABLE	9004346	SMD1X3XO9M	NA
POWDERED CELLULOSE	ORAL	TABLET, COATED	9004346	SMD1X3XO9M	40.2mg

POWDERED CELLULOSE	ORAL	TABLET, DELAYED RELEASE	9004346	SMD1X3XO9M	16mg
POWDERED CELLULOSE	ORAL	TABLET, EXTENDED RELEASE	9004346	SMD1X3XO9M	110.6mg
POWDERED CELLULOSE	ORAL	TABLET, FILM COATED	9004346	SMD1X3XO9M	391.7mg
POWDERED CELLULOSE	ORAL	TABLET, FILM COATED, EXTENDED RELEASE	9004346	SMD1X3XO9M	42.25mg
POWDERED CELLULOSE	SUBLINGUAL	TABLET	9004346	SMD1X3XO9M	4.5mg
POWDERED CELLULOSE	TOPICAL	DISC	9004346	SMD1X3XO9M	NA

As taken from FDA, 2019c

4. Metabolism/Pharmacokinetics

4.1. Metabolism/metabolites

“A double-blind cross-over trial of the effects of guar gum and microcrystalline cellulose on metabolic control and serum lipids in 22 Type 2 diabetic patients has been carried out. The fibre preparations were given at 15 g/day for a 2-week period and then at 5 g/day for the remaining 10-week period of each treatment phase. There was no effect of the microcrystalline cellulose diet on fasting blood glucose level, glycosylated haemoglobin, serum HDL-cholesterol, serum triglycerides, serum zinc or ferritin, or urinary magnesium excretion” As taken from WHO Food Additives Series 40 available at http://www.inchem.org/documents/jecfa/jecmono/v040je03.htm

4.2. Absorption, distribution and excretion

“Groups of male and female Sprague-Dawley CD rats (20 per group) from Charles River Laboratories were administered, by gavage, suspensions of a special fine particle-size

microcrystalline cellulose (median particle size 6 µm). The rats were dosed orally daily for 90 consecutive days at a level of 5000 mg/kg bw per day by means of a 25% suspension in tap water. The animals were killed on study days 91-94 and necropsies were carried out under conditions that reduced the possibility of contamination of tissues with fine particulates. The birefringent microcrystalline cellulose particles were not detected in any organ or tissue, including gut-associated lymphoid tissue, liver, lung, spleen and brain."

"In another study, dyed plant foods (oatmeal, creamed corn) were fed to human subjects, and blood and urine were examined for coloured fibres. Dyed fibres were shown to be present (Schreiber, 1974). Lycopodium spores and pollen grains have also been shown to be persorbed by humans"

"Rats, pigs and dogs were used to study the persorption of microcrystalline cellulose. The animals were not fed for 12 hours prior to oral administration of the test compound. Rats, dogs and pigs were given 0.5, 140 and 200 g, respectively, of the test compound. Venous blood was taken from the animals 1-2 hours after administration of the test compound, and examined for particles. Persorbed particles were demonstrated in the blood of all three species. The average maximum diameter for persorbed particles was greater in rats than in dogs or pigs"

"In another study, eight healthy males received 30 g microcrystalline cellulose daily as supplement to their diet for 15 days. D-xylose absorption varied between pretest, test and post-test periods, being lower during microcrystalline cellulose ingestion. The absorption of 131I-triolein was unaffected by microcrystalline cellulose ingestion. No change was noted in the faecal flora nor was there any significant effect on blood chemistry during ingestion of microcrystalline cellulose. Examination of urine, blood and faecal levels of vitamin B1 during microcrystalline cellulose ingestion showed no difference from control periods"

"Four rats were fed 14C-labelled microcrystalline cellulose at 10 or 20% of their diet. No evidence of degradation or digestion was noted. Faecal recoveries of radioactivity ranged from 96-104% and were complete for all labelled material. No radioactivity appeared in the urine"

"One human subject received 150 g of microcrystalline cellulose daily in two portions for a 15-day adaptation period. He then received 14C-labelled microcrystalline cellulose (47.6 µCi) in two portions on one day. Supplementation of the diet with unlabelled microcrystalline cellulose continued for 10 days. Twenty-four-hour faecal and urine collections were examined for radioactivity. No radioactivity appeared in the urine or in the expired CO2. All administered radioactivity (98.9 ± 3.0%) was recovered from the faeces within two days"

"Most (87%) of the radiolabel associated with 131II-labelled alpha-cellulose fibres (retained by a sieve with pores of 1 mm diam) was excreted by 4 male and 4 female volunteers within 5 days of ingestion. Less than 2% of the faecal radiolabel was unbound; urinary excretion of unbound radio-iodine accounted for another 1.9% of the total dose" As taken from WHO Food Additives Series 40 available at http://www.inchem.org/documents/jecfa/jecmono/v040je03.htm

"Animal and human data clearly demonstrated that microcrystalline cellulose (E 460(i)) and powdered cellulose (E 460(ii)) are not absorbed intact in the gastrointestinal tract and could

be fermented during their passage through the large intestine by strains of bacteria found in the human colon."

"The Panel noted that microcrystalline, powdered and modified celluloses would not be absorbed intact and would be less fermented than other polysaccharides such as gums, starches or pectins."

As taken from EFSA, 2018

4.3. Interactions

"The aspects of dietary fibers' and different food ingredients' interaction are considered in this article; in particular, the questions of dietary fibers' interaction with the main foodstuff components (proteins, fats, vitamins, etc.), especially functional purpose; and the interaction of microcrystalline cellulose (MCC), which is part of dietary fiber, with the main foodstuff components--protein, vitamins and antioxidants (tocopherol, and riboflavin). It was found that with increasing of MCC content in the diet, there was increase of vitamins sorption (especially tocopherol), with its maximum at 3 g of MCC. This is probably due to the relatively high porosity and properties of MCC to absorb and retain water, lipids and other food ingredients. These findings point to the need to consider the possibility of sorption of polysaccharides and, in particular in the preparation of starch-rich foods and dietary recommendations for their use". As taken from Bessonov W et al. (2012). Voprosy Pitaniia 81, 41-5. PubMed 2013, available at http://www.ncbi.nlm.nih.gov/pubmed/22888670?dopt=AbstractPlus

5. Toxicity

5.1. Single dose toxicity

Organism	Test Type	Route	Reported Dose (Normalized Dose)	Effect	Source
rabbit	LD50	skin	> 2gm/kg (2000mg/kg)		Toxicology Letters. Vol. (Suppl), Pg. 243, 1992.
rat	LC50	inhalation	> 5800mg/m3/4H (5800mg/m3)		Toxicology Letters. Vol. (Suppl), Pg. 243, 1992.
rat	LD50	intraperitoneal	> 31600mg/kg (31600mg/kg)		FAO Nutrition Meetings Report Series. Vol. 50A, Pg. 83, 1972.
rat	LD50	oral	> 5gm/kg (5000mg/kg)		Toxicology Letters. Vol. (Suppl), Pg. 243, 1992.

As taken from ChemIDplus, available at https://chem.nlm.nih.gov/chemidplus/

Type of Test	Route of Exposure	Species Observed	Dose Data	Toxic Effects	Reference
TDLo - Lowest published toxic dose	Oral	Rodent - rat	120 gm/kg	Gastrointestinal - hypermotility, diarrhea Gastrointestinal - other changes	EPASR* United States Environmental Protection Agency, Office of Pesticides and Toxic Substances. (U.S. Environmental Protection Agency, 401 M St., SW, Washington, DC 20460) History unknown. Volume(issue)/page/year: #86940001000,1994

As taken from RTECS, 2017

Species	Sex	Route	LD_{50} (g/kg bw)
Rat	M	Oral	>3.16
Rat	M+F	Oral	>5.00
Rat	M+F	Oral	>5.00
Rat	M	Intraperitoneal	>3.16
Rat	M+F	Dermal	>2.00
Rat	M+F	Dermal	>2.00
Rabit	M+F	Dermal	>2.00

Species	Sex	Route	LC_{50} (g/litre)
Rat	M+F	Inhalation	>5.35-5.8

“[…] there was no evidence of toxicity of microcrystalline cellulose preparations administered either orally or dermally to rats at doses of 5000 or 2000 mg/kg bw, respectively. The observations seen at necropsy in animals treated intraperitoneally with Cellan 300 at 3160 mg/kg bw are consistent with an irritant reaction caused by the presence of foreign material. An inhalation toxicity study showed only transient effects at a concentration of 5.35 mg/litre.”

“Groups of five male Sprague-Dawley rats received a single oral dose, by stomach tube, of 10.0, 31.6, 100, 316, 1000 or 3160 mg/kg bw of a suspension of Cellan 300 (refined alpha-cellulose) in either distilled water or Mazola corn oil. The animals were observed for 7 days following administration. No differences were observed among the groups as regards the average body weight, appearance and behaviour compared to untreated rats. No observable gross pathology was revealed at autopsy in animals dosed with either suspension. Therefore, the acute oral LD50 was >3160 mg/kg” “Similar single doses of refined alpha-cellulose were given i.p. in distilled water suspension to five male rats. During 7 days observation there were no abnormalities in the rats given 316 mg/kg bw or less. At 1000 and 3160 mg/kg bw inactivity, laboured respiration and ataxia were observed 10 min after administration and, at 3160 mg/kg bw, ptosis and sprawling of the limbs were

observed. These animals appeared normal after 24 hours and for the remainder of the observation period. At sacrifice body weights were higher than normal and gross autopsy revealed adhesions between the liver, diaphragm and peritoneal wall and congestion of the kidneys. Masses resembling unabsorbed compound were also observed and these were found to a small extent in the mesentery of the animals administered 316 mg/kg bw. There were no deaths and therefore the acute i.p. LD50 was >3160 mg/kg bw" "Ten male and ten female Sprague-Dawley rats fasted overnight were fed Avicel RCN-15 (a mixture of 85% microcrystalline cellulose with 15% guar gum) at a dose level of 5000 mg/kg bw mixed with parmesan cheese. Six of ten males and five of ten females consumed the mixture within 24 hours. After a 14-day period during which all rats gained weight normally they were killed. There were no gross lesions at necropsy. Under the specified conditions of administration the LD50 was >5000 mg/kg bw" As taken from WHO Food Additives Series 40 available at http://www.inchem.org/documents/jecfa/jecmono/v040je03.htm

"The acute toxicity, cytotoxicity, genotoxicity and antigenotoxic effects of BC were studied. Cytotoxicity of BC was evaluated in cultured C3A hepatoma cells (HepG2/C3A) using a lactate dehydrogenase (LDH) activity assay. Acute toxicity was tested in adults Wistar rats treated with a single dose of BC. The genotoxicity of BC was evaluated in vivo by the micronucleus assay. BC (0.33-170 µg/mL) added to C3A cell culture medium caused no elevation in LDH release over the background level recorded in untreated cell wells. The treatment with the BC in a single oral dose (2000 mg/kg body weight) caused no deaths or signs of toxicity. BC attenuated CP-induced and inhibition the incidence of MNPCE (female: 46.94%; male: 22.7%) and increased the ratio of PCE/NCE (female: 46.10%; male: 35.25%). There was no alteration in the LDH release in the wells where C3A cells were treated with increasing concentrations of BC compared to the wells where the cells received the cell culture medium only (background of approximately 20% cell death), indicated that in the dose range tested BC was not cytotoxic. BC was not cytotoxic, genotoxic or acutely toxic. BC attenuated CP-induced genotoxic and myelotoxic effects." As taken from Pinto FC et al. 2016. Carbohydr. Polym. 137, 556-60. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/26686163

"Bacterial cellulose (BC) is a biopolymer synthesized by certain acetic acid bacteria strains. The safety of BC regarding its potential use in food applications is here reviewed. The acute, sub-acute and subchronic oral toxicity assays showed that consumption of BC had no adverse effects in rats. Several studies demonstrated that BC is not genotoxic, did not induce chromosomal aberrations in CHO cells under both non-activating and metabolic activating conditions, is inactive in the in vitro Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay, had no reproductive toxicity in mice and exerted no embryotoxicity and teratogenicity effects in rats. Several studies on the BC in biomedical applications further reinforces its safety: a primary eye and dermal irritation studies in the rabbit showed that BC was non-irritating. The inflammatory reaction to subcutaneously implanted BC has been evaluated in animal models and for different periods of time, demonstrating that BC is biocompatible and does not trigger a harsh inflammatory reaction. Altogether, and considering its longstanding history of human consumption in Asian countries, as well as its utilization in biomedical devices, it may be concluded that BC is safe for applications in food technology." As taken from Dourado F et al. 2017. Toxicol. Rep. 4, 543-553. PubMed, 2018 available at https://www.ncbi.nlm.nih.gov/pubmed/29090119

“Data on acute oral toxicity are available for microcrystalline cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose and sodium carboxy methyl cellulose. These indicate a low oral acute toxicity.”

As taken from EFSA, 2018

5.2. Repeated dose toxicity

“Groups of four male rats were kept on diets containing 0.25, 2.5 or 25% of various edible celluloses for 3 months. No differences were observed among the groups with regard to growth and faecal output. Histopathology of the gastrointestinal tract revealed no treatment-related abnormalities”

“Three groups of five male rats received 0.5 or 10% microcrystalline cellulose in their diet for 8 weeks. Growth was comparable to controls but the 10% group showed slightly lower body weights. Haematology, serum chemistry and vitamin B1 levels in blood and faeces showed no differences from controls”

“Groups of five male weanling Sprague-Dawley rats received 0, 5, 10 or 20% of acid-washed cellulose in their diet during three consecutive nutrient balance trials over a period of 17 days. Absorption of magnesium and zinc were significantly lower in the animals that were receiving the 10 and 20% cellulose diets. Histopathology of the gastrointestinal tract revealed increased mitotic activity and the presence of increased numbers of neutrophils in crypt epithelial cells, particularly of the duodenum and jejunum”

“A mixture of four types of Elceme (in the ratio of 1:1:1:1) was fed to groups of Wistar rats for 30 days at a dietary level of 50%, and for 90 days at a dietary level of 10% (Elceme is a microcrystalline cellulose, and the four types are identified by particle size, namely, 1-50 (powder), 1-100 (powder), 1-150 (fibrillar), 90-250 (granulate)). All test animals were observed for food intake and weight gain. For animals in the 10% group, urinalysis, haematological tests and serum biochemical tests were carried out at weeks 6 and 13 of the test. A complete autopsy including histopathology was carried out at the end of the study. Animals in the 50% group were subjected to a persorption test, on the last day of the study, by addition of a cellulose staining dye (Renal, Wine-red) to the food of the test animals at a level equivalent to 5% of the Elceme. The animals were sacrificed 24 hours after administration of the diet, and a careful histological examination was made of the gastrointestinal tract, spleen, liver, kidney and heart for stained particles. Animals in the 10% group gained significantly less weight than those in the control group; the marked decrease commenced in the third or fourth week of the study. Food intake was similar in test and control groups. Urinalysis, haematological values and biochemical values were similar for test and control group 1. At autopsy some of the rats on the test diet had distended stomachs, which often contained considerable amounts of the test diet. The absolute liver and kidney weights and the ratio of the weight of these organs to brain weight was increased in test animals when compared with control animals. No compound-related pathology was reported. Animals in the 50% group showed considerable less weight gain than control animals in spite of a marked increase in food consumption. No persorption of dyed fibres was observed”

“Randomly bred rats of both sexes were divided into groups that received a control diet or the control diet with 330 mg/kg microcrystalline cellulose for a period of 6 months. Six rats in each group were then killed, their organs were examined, and tissues were taken for histopathology. No effects of the treatment were observed”

“Groups of Crl:CD(R) BR/VAF/Plus rats (20/sex per group) were administered 0 (control), 25 000 or 50 000 mg/kg Avicel RCN-15 in the diet for 90 days. A few test animals were noted as having chromodacryorrhea/ chromorhinorrhea, but this was not considered to be biologically significant. In some early weeks the rats increased diet consumption, probably to allow for the increased dietary fibre content. Body weight gain was unaffected. During the study and at necropsy there was no evidence of treatment-related changes. Clinical chemistry, haematology and organ weights were unaffected by treatment. Histopathology of 34 organs or tissues, including gastrointestinal tract and gut-associated lymphoid tissue of the ileum, provided no evidence of toxicity of microcrystalline cellulose. The calculated daily consumption of microcrystalline cellulose was 3769 mg/kg bw per day for males and 4446 mg/kg bw per day for females. The author noted that the NOEL exceeded 50 000 mg/kgdiet”

“Three groups of 50 male and 50 female rats received in their diet for 72 weeks either 30% ordinary cellulose or dry microcrystalline cellulose or micro-crystalline cellulose gel. Appearance and behaviour was comparable in all groups. No adverse effects were noted. The body weights of males given microcrystalline cellulose gel were higher than those of the controls. Food efficiency, survival and haematology were comparable in all groups. The liver and kidney weights of males receiving microcrystalline cellulose gel were higher than the controls. Gross and histopathology showed some dystrophic calcification of renal tubules in females on microcrystalline cellulose but all other organs appeared unremarkable. Tumour incidence did not differ between the groups”

More studies have been done in which a group of rats was fed with a normal diet was compared to a second one fed with microcrystalline cellulose. The general conclusion is that cellulose addition to the normal diet has no effects on body weight (sometimes just a little weight gain for male rats in some studies), food consumption.

As taken from WHO Food Additives Series 40 available at http://www.inchem.org/documents/jecfa/jecmono/v040je03.htm

“The lung-damaging effect of intratracheally administered cellulose was studied by biochemical and histological methods. Cell count, protein, phospholipid, lactate dehydrogenase and acid phosphatase were determined in bronchoalveolar lavage fluid 1, 3 and 7 days after intratracheal instillation. Histological tests were performed after days 1, 3 and 30. In vitro, cellulose did not damage the macrophage cells. In vivo, interstitial oedema as well as the initial signs of inflammation could be detected in the lung after the first day. Inflammation after 1 week could be noted, partly interstitial and partly intra-alveolar and intrabronchial. In the bronchoalveolar lavage fluid, protein, lactate dehydrogenase, acid phosphatase, phospholipid and cell count were enhanced after days 1 and 3. After 1 month, the developing bronchioalveolitis is fibrous in character. Contrary to the in vivo study, cellulose did not damage rat peritoneal macrophages” (Adamis et al. 1997).

Type of Test	Route of Exposure	Species Observed	Dose Data	Toxic Effects	Reference
TDLo - Lowest published toxic dose	Oral	Rodent - rat	420 gm/kg/4W (continuous)	Gastrointestinal - other changes Nutritional and Gross Metabolic - weight loss or decreased weight gain	AJPHAP American Journal of Physiology. (American Physiological Soc., 9650 Rockville Pike, Bethesda, MD 20814) V.1- 1898- Volume(issue)/page/year: 188,550,1957
TDLo - Lowest published toxic dose	Oral	Rodent - rat	159 gm/kg/90D (intermittent)	Nutritional and Gross Metabolic - weight loss or decreased weight gain	TOXID9 Toxicologist. (Soc. of Toxicology, Inc., 475 Wolf Ledge Parkway, Akron, OH 44311) V.1- 1981- Volume(issue)/page/year: 90,346,2006
TDLo - Lowest published toxic dose	Oral	Rodent - rat	56000 mg/kg/8W (intermittent)	Blood - thrombocytopenia Blood - other changes Blood - changes in other cell count (unspecified)	TOVEFN Toksikologicheskii Vestnik. (18-20 Vadkovskii per. Moscow, 101479, Russia) History Unknown Volume(issue)/page/year: (4),34,2007
TDLo - Lowest published toxic dose	Oral	Rodent - rat	56000 mg/kg/8W (intermittent)	Blood - thrombocytopenia Blood - changes in other cell count (unspecified)	TOVEFN Toksikologicheskii Vestnik. (18-20 Vadkovskii per. Moscow, 101479, Russia) History Unknown Volume(issue)/page/year: (4),34,2007
TDLo - Lowest published toxic dose	Oral	Rodent - rat	112000 mg/kg/8W (intermittent)	Blood - other changes	TOVEFN Toksikologicheskii Vestnik. (18-20 Vadkovskii per. Moscow, 101479, Russia) History Unknown Volume(issue)/page/year: (4),34,2007

TDLo - Lowest published toxic dose	Oral	Rodent - rat	11200 mg/kg/8W (intermittent)	Blood - change in clotting factors	TOVEFN Toksikologicheskii Vestnik. (18-20 Vadkovskii per. Moscow, 101479, Russia) History Unknown Volume(issue)/page/year: (4),34,2007

As taken from RTECS, 2017

“Short-term and subchronic toxicity studies have been performed with microcrystalline cellulose (E 460(i)), methyl cellulose (E 461), ethyl cellulose (E 462), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464), sodium carboxy methyl cellulose (E 466) and enzymatically hydrolysed carboxy methyl cellulose (E 469). In the majority of studies, animals were dosed via diet at levels up to 10%. Effects on body weight at the highest dose tested (10%) were reported in some, but not all studies, which may reflect nutritional constraints rather than toxicity. No adverse effects were reported with most of the tested celluloses, except for local effects on caecal size due to the presence of undigested fibre.”

“Chronic toxicity studies have been performed with microcrystalline cellulose (E 460(i)), methyl cellulose (E 461), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464), ethyl methyl cellulose (E 465) and sodium carboxy methyl cellulose (E 466). Although there were some inconsistencies in the data, the main effects seen were decreases in body weight gain at the highest dose, which are likely to be due to the amount/bulk of celluloses in the diet leading to nutritional imbalance. Furthermore, in a chronic feeding study with microcrystalline cellulose (E 460(i)), some dystrophic calcification of renal tubules was observed in the high dose group (15,000 mg/kg bw per day). The no observed adverse effect level (NOAEL) values reported ranged up to 9,000 mg/kg bw per day.”

“There was evidence that repeated doses up to 35 g/person of microcrystalline cellulose or powdered cellulose did not adversely affect clinical chemistry and haematological parameters and had no effect on the absorption and/or the metabolism of dietary constituents.”

“The Panel considered that based on the animal data, the toxicity of microcrystalline, powdered and modified celluloses was low and that NOAELs were generally the highest dose tested (up to at least 9,000 mg/kg bw per day). In addition, the large cumulative group of exposed animals from use in control populations to 2% would indicate that there. There were no reasons why humans would be expected to be more sensitive than animals in toxicodynamics or. The available data in humans indicate that daily doses of up to 6,000 mg for around 8 months were not associated with adverse effects; however in line with many other dietary fibres, large bolus intakes of celluloses were occasionally associated with laxation, but there was a lack of dose–response data available.”

As taken from EFSA, 2018

5.3. Reproduction toxicity

“Groups of eight male and 16 female rats were used to produce P, F_{1a}, F_{1b}, F_2 and F_3 generations after having been fed on diets containing 30% crystalline cellulose flour or gel or ordinary cellulose as a control. The presence in the diet of such an amount of non-nutritious material, which contributed no calories, had an adverse effect on reproduction. Fertility and numbers of live pups were relatively depressed, and lactation performances in all three generations, as well as survival and the physical condition of the pups, were unsatisfactory throughout the study. The new-born pups appeared smaller, weak and showed evidence of disturbed motor coordination. Liver weights were increased in the group receiving microcrystalline cellulose gel in all generations but other organ weights showed no consistent patterns. […]

“Seventy-two rats (Sprague-Dawley CD) divided into eight groups were fed a mixture of four types of Elceme in the ratio of 1:1:1:1 in the diet at a level of 0, 2.5, 5 or 10% for 10 days, between days 6 and 15 of pregnancy. Rats of four test groups were killed on day 21 of pregnancy and the following parameters studied: number of fetuses and resorption sites, litter size and average weight of rats, average weight of fetuses and average backbone length. Fetuses were also examined for soft tissue or skeletal defects. The remaining groups were allowed to bear young, which were maintained to weaning (21 days). The following parameters were studied: litter size, weight of pups at days 7 and 21, and there was a histological study of the offspring. Although there is some suggestion that administration of dietary Elceme resulted in a dose-dependent increase in resorption sites, as well as a change in sex ratio, and possible defects such as opaque crystalline lenses, the data has not been presented in a manner that permits a meaningful interpretation. However, the author concluded that Elceme is non-teratogenic” “Groups of 25 presumed pregnant Crl:CD(R) BR VAF/Plus rats were administered 0 (control), 25 000 or 50 000 mg Avicel RCN-15/kg diet (equal to 2.1 and 4.5 g/kg bw per day, respectively) *ad libitum* on days 6 to 15 of gestation. Animals received basal diet at all other times. In the group receiving 50 000 mg/kg the food consumption on days 6 to 15 was significantly higher than that of controls, probably because of the increased fibre content. On day 20 of gestation the dams were killed by carbon dioxide inhalation and the following parameters studied: number and distribution of implantation sites, early and late resorptions, live and dead fetuses and corpora lutea. External, visceral and skeletal examinations of the fetuses were also performed. There was no evidence of any adverse effects of the test material on either the dams or the fetuses.” “[…] The parameters studied and examinations performed were the same as in the study of Freeman (1992b). There was no evidence of any effects of the Avicel treatment on the fetuses, and there was no evidence of a change of sex ratio in the pups or of eye defects. Under the conditions of the study, the maternal and fetal NOEL was > 50 000 mg/kg diet (equal to 4.6 g/kg bw per day)”

“At autopsy female rats of all generations showed kidney changes comprising pitting, occasional enlargement and zonation of the cortex. Other organs showed no consistent changes. No teratological deformities were seen”

As taken from WHO Food Additives Series 40 available at http://www.inchem.org/documents/jecfa/jecmono/v040je03.htm

“No adverse effects were found on reproduction or neonate development in rats and mice. Therefore, no adverse health effects in humans are expected from exposure to purified cellulose.” As taken from Anderson RL et al. Cancer Lett., 1992, Apr 15, 63(2):83-92. PubMed, 2009 available at

http://www.ncbi.nlm.nih.gov/entrez/query.fcgicmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=1562993&query_hl=30&itool=pubmed_docsum

“Maternal diet during pregnancy has been proposed to modify female offspring's later susceptibility to develop breast cancer; however, most of the dietary factors identified thus far have led to increased risk. To identify dietary factors that might reduce offspring's breast cancer risk, pregnant rat dams were fed diets containing 6% fiber originating either from cellulose (control), or oat, whole wheat or defatted flax flour. At birth, dams were switched to the AIN93 semi-purified diet. Mammary tumor incidence and multiplicity, induced by administering the offspring 5 mg 7,12-dimethylbenz[a]anthracene (DMBA) at the age of 50 days, was reduced in the whole wheat flour-exposed offspring and increased in the defatted flax-exposed offspring. To identify the mechanisms mediating the effects of in utero dietary exposures, changes in mammary gland morphology and gene expression were assessed before puberty onset (3 weeks of age) and at the time rats are most susceptible to malignant transformation (8 weeks of age). The number of terminal end buds (TEBs), i.e., the targets of malignant transformation, was reduced in the mammary glands of whole wheat- and oat flour-exposed offspring, as compared to the controls. Further, the number of apoptotic epithelial cells (based on ISOL assay) was elevated in the whole wheat flour offspring, but no changes in cell proliferation (PCNA), estrogen receptor alpha (ER-alpha) or cyclin D1 mRNA or protein levels were seen. The mRNA and/or protein levels of BRCA1 and p53 were significantly increased in the mammary glands of whole wheat flour offspring. Further, the levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG), a marker of DNA damage, were significantly reduced in these rats, suggesting that maternal dietary exposure to whole wheat during pregnancy may reduce offspring's breast cancer risk by improving DNA damage repair mechanisms”. As taken from Yu B; Khan G; Foxworth A; Huang K; Hilakivi-Clarke L Int J Cancer. 2006, Nov 15; 119(10):2279-86. PubMed, 2009 available at http://www.ncbi.nlm.nih.gov/pubmed/16921499

“Concerning reproductive and developmental toxicity, data are available for microcrystalline cellulose (E 460(i)), methyl cellulose (E 461), hydroxypropyl cellulose (E 463) and sodium carboxy methyl cellulose (E 466). The substances were tested in mice, rats, hamsters and/or rabbits with oral dosing via gavage (FDLI, 1973, 1975; Ferch, 1973a,b; Cannon Labs, 1975, 1977; Kitagawa et al., 1978a,b; Fritz and Becker, 1981; Freeman, 1992b). Adverse effects on reproductive performance or developmental effects were not observed with modified and unmodified celluloses at doses greater than 1,000 mg/kg bw by gavage (often the highest dose tested).”

As taken from EFSA, 2018

5.4. Mutagenicity

“Various microcrystalline cellulose preparations have been tested for genotoxicity in several different assay systems. The results, all of which were negative” As taken from WHO Food Additives Series 40 available at http://www.inchem.org/documents/jecfa/jecmono/v040je03.htm

Test system	Test cells	Concentration	Results	Reference
Reverse mutation [1,2]	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	50-5000 µg/plate	negative	Batt, 1992
Reverse mutation [1,3]	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	10-5000 µg/plate	negative	Lawlor, 1996
Reverse mutation [1,3]	Escherichia coli WP2uvrA	10-5000 µg/plate	negative	Lawlor, 1996
Forward mutation [1,2]	Mouse lymphoma L5178Y cells, TK locus	100-1000 µg/ml	negative	Cifone, 1992
Forward mutation [1,4]	Mouse lymphoma L5178Y cells, TK locus	125-1000 µg/ml	negative	Cifone, 1994
UDS with confirmatory assay [2]	Rat liver primary cell cultures	10-1000 µg/ml	inactive	McKeon, 1992
In vivo mammalian micronucleus assay [2, 5]	Bone marrow polychromatic erythrocytes of ICR mice	5000 mg/kg bw, oral	negative	Murli, 1992
In vivo mammalian micronucleus assay [6]	Bone marrow erythrocytes polychromatic of CD-1 (ICR) mice	5000 mg/kg bw, oral	negative	Murli, 1994a
In vivo mammalian micronucleus assay [4]	Bone marrow polychromatic erythrocytes of CD-1 (ICR) mice	5000 mg/kg bw, oral	negative	Murli, 1994b

1 With and without rat liver S9 metabolic activation

2 Test material: Avicel RCN-15

3 Test material: Avicel AC-815

4 Test material: Avicel CL-611
5 Test material: Avicel RCN-15
6 Test material: Avicel PH101 Pharmaceutical"

In the reverse mutation assays the microcrystalline cellulose formulations produced a heavy precipitate on the plate at the highest concentration. Solubility also affected the forward mutation assays and it was not possible to include concentrations of the test material that were cytotoxic.

As taken from WHO Food Additives Series 40 available at http://www.inchem.org/documents/jecfa/jecmono/v040je03.htm

In vivo **Genotoxicity:**

In the *in vivo* mammalian micronucleus assays it is improbable that there was appreciable persorption of the test materials, and, therefore, there was little exposure of the bone marrow cells. In the test in which Avicel RCN-15 was used it was administered admixed with the diet of male and female ICR mice. Only mice that had consumed all the diet within 10 hours were retained in the study and were killed after 24, 48 or 72 hours. Because one group of control mice had 0 micronuclei per 1000 polychromatic erythrocytes, the comparison with the test group was statistically significant. This was not considered to be a valid observation. There is no evidence that microcrystalline cellulose is genotoxic.

As taken from WHO Food Additives Series 40 available at http://www.inchem.org/documents/jecfa/jecmono/v040je03.htm

“Nanocellulosics are among the most promising innovations for a wide-variety of applications in materials science. Although nanocellulose is presently produced only on a small scale, its possible toxic effects should be investigated at this early stage. The aim of the present study was to examine the potential genotoxicity and immunotoxicity of two celluloses in vitro - cellulose nanocrystals (CNC; mean fibril length 135 nm, mean width 7.3 nm) and a commercially available microcrystalline (non-nanoscale) cellulose (MCC; particle size ~50 µm). Both celluloses showed 55% cytotoxicity at approximately 100 µg/ml after 4-h, 24-h, and 48-h treatment of human bronchial epithelial BEAS 2B cells, as determined by luminometric detection of ATP and cell count (dead cells identified by propidium iodide). Neither of the materials was able to induce micronuclei (MN) in binucleate or mononucleate BEAS 2B cells after a 48-h treatment (2.5-100 µg/ml). In human monocyte-derived macrophages, MCC induced a release (measured by enzyme-linked immunosorbent assay; ELISA) of the pro-inflammatory cytokines tumor necrosis factor α (TNF-α) and (after lipopolysaccharide-priming) interleukin 1β (IL-1β) after a 6-h exposure to a dose of 300 µg/ml, but CNC (30-300 µg/ml) did not. In conclusion, our results show that nanosized CNC is neither genotoxic nor immunotoxic under the conditions tested, whereas non-nanosized MCC is able to induce an inflammatory response. More studies are needed, especially in vivo, to further assess if CNC and other nanocelluloses induce secondary genotoxic effects mediated by inflammation.” As taken from Catalán J et al. 2015. Environ. Mol. Mutagen. 56(2), 171-182. PubMed, 2016 available at http://www.ncbi.nlm.nih.gov/pubmed/25257801

“The acute toxicity, cytotoxicity, genotoxicity and antigenotoxic effects of BC were studied. Cytotoxicity of BC was evaluated in cultured C3A hepatoma cells (HepG2/C3A) using a lactate dehydrogenase (LDH) activity assay. Acute toxicity was tested in adults Wistar rats treated with a single dose of BC. The genotoxicity of BC was evaluated in vivo by the micronucleus assay. BC (0.33-170 μg/mL) added to C3A cell culture medium caused no elevation in LDH release over the background level recorded in untreated cell wells. The treatment with the BC in a single oral dose (2000 mg/kg body weight) caused no deaths or signs of toxicity. BC attenuated CP-induced and inhibition the incidence of MNPCE (female: 46.94%; male: 22.7%) and increased the ratio of PCE/NCE (female: 46.10%; male: 35.25%). There was no alteration in the LDH release in the wells where C3A cells were treated with increasing concentrations of BC compared to the wells where the cells received the cell culture medium only (background of approximately 20% cell death), indicated that in the dose range tested BC was not cytotoxic. BC was not cytotoxic, genotoxic or acutely toxic. BC attenuated CP-induced genotoxic and myelotoxic effects.” As taken from Pinto FC et al. 2016. Carbohydr. Polym. 137, 556-60. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/26686163

“Avicel® RCN-15 (a mixture of 85% microcrystalline cellulose with 15% guar gum) did not induce mutagenic effects in the presence or absence of a metabolic activation system in bacterial reverse mutation assays (Batt, 1992), in a gene mutation assay in mouse lymphoma cells (at thymidine kinase locus) (Cifone, 1992), in an in vitro test for unscheduled DNA synthesis (McKeon, 1992) and in the mouse bone marrow micronucleus assays (Murli, 1992). Negative results were also reported with other microcrystalline cellulose preparations in other unpublished studies (Documentation provided to EFSA no. 34, 35, 36, 37). Overall, the Panel concluded that microcrystalline cellulose (E 460(i)) and powdered cellulose (E 460(ii)), which only differs for polymerisation degree, do not raise concern for genotoxicity.”

As taken from EFSA, 2018

5.5. Cytotoxicity

“.....Contrary to the in vivo study, cellulose did not damage rat peritoneal macrophages (Adamis et al. 1997).

“Cellulose nanofibers (CNF) have mechanical properties that make them very attractive for applications in the construction of polymeric matrices, drug delivery and tissue engineering. However, little is known about their impact on mammalian cells. The objective of this study was to evaluate the cytotoxicity of CNF and their effect on gene expression of fibroblasts cultured in vitro. The morphology of CNF was analyzed by transmission electron microscopy and the surface charge by Zeta potential. Cell viability was analyzed by flow cytometry assay and gene expression of biomarkers focused on cell stress response such as Heat shock protein 70.1 (HSP70.1) and Peroxiredoxin 1 (PRDX1) and apoptosis as B-cell leukemia (BCL-2) and BCL-2 associated X protein (BAX) by RT-PCR assay. Low concentrations of CNF (0.02-100 μg ml(-1)) did not cause cell death; however, at concentrations above 200 μg ml(-1), the nanofibers significantly decreased cell viability (86.41 ± 5.37%). The exposure to high concentrations of CNF (2000 and 5000 μg ml(-1)) resulted in increased HSP70.1, PRDX1 and BAX gene expression. The current study

concludes that, under the conditions tested, high concentrations (2000 and 5000 µg ml(-1)) of CNF cause decreased cell viability and affect the expression of stress- and apoptosis-associated molecular markers." As taken from Pereira MM et al. 2013. Nanotechnology 24(7), 075103. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/23358497?dopt=AbstractPlus

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"The acute toxicity, cytotoxicity, genotoxicity and antigenotoxic effects of BC were studied. Cytotoxicity of BC was evaluated in cultured C3A hepatoma cells (HepG2/C3A) using a lactate dehydrogenase (LDH) activity assay. Acute toxicity was tested in adults Wistar rats treated with a single dose of BC. The genotoxicity of BC was evaluated in vivo by the micronucleus assay. BC (0.33-170 µg/mL) added to C3A cell culture medium caused no elevation in LDH release over the background level recorded in untreated cell wells. The treatment with the BC in a single oral dose (2000 mg/kg body weight) caused no deaths or signs of toxicity. BC attenuated CP-induced and inhibition the incidence of MNPCE (female: 46.94%; male: 22.7%) and increased the ratio of PCE/NCE (female: 46.10%; male: 35.25%). There was no alteration in the LDH release in the wells where C3A cells were treated with increasing concentrations of BC compared to the wells where the cells received the cell culture medium only (background of approximately 20% cell death), indicated that in the dose range tested BC was not cytotoxic. BC was not cytotoxic, genotoxic or acutely toxic. BC attenuated CP-induced genotoxic and myelotoxic effects." As taken from Pinto FC et al. 2016. Carbohydr. Polym. 137, 556-60. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/26686163

5.6. Carcinogenicity

"The effect of artifical diets containing varied concentrations of either wheat bran or pure cellulose fibre on the induction of mammary tumours by *N*-nitrosomethylurea (i.v., 40 mg/kg) was studied in female F344 rats. The wheat bran diet appeared to possess anti-promotion properties that pure cellulose lacked. The concentrations of serum estrogens, urinary estrogens and faecal estrogens did not vary in a consistent, statistically significant manner"

"The effect of a high-fibre diet containing 45 000 mg/kg Avicel PH-105 on the development of colon tumours was investigated in male Wistar rats that were injected with 1,2-dimethylhydrazine dihydrochloride (25 mg/kg, s.c., once weekly for 16 weeks). The test and control diets were administered for 2 weeks prior to the first injection of the carcinogen.

There was a reduction in the number of animals bearing colon tumours and a statistically significant reduction in the number of colon tumours/rat in the high-fibre dietary group. However, for small bowel tumours and tumours of the ear canal there was no significant difference between the dietary groups"

"Similarly, microcrystalline cellulose has been associated with the formation of granulomas in human lung when it has been injected intravenously during drug abuse. No such lesions have been described as a consequence of oral igestion of microcrystalline cellulose by rats or humans." As taken from WHO Food Additives Series 40 available at http://www.inchem.org/documents/jecfa/jecmono/v040je03.htm

Species:	RAT
Strain/Sex:	F344/FEMALE
Route:	SUBCUTANEOUS IMPLANT
Dose:	10 X 20 X 0.3 MM SHEETS IMPLANTED INTO 2 SITES IN LATERAL ABDOMINAL REGION AND 1 SITE ON THE BACK (STUDY DURATION: 741 D)
Results:	NEGATIVE
Reference:	[HATANAKA,S, ONEDA,S, OKAZAKI,K, SHONG,L, YOSHIDA,A, ISAKA,H AND YOSHIDA,H; INDUCTION OF MALIGNANT FIBROUS HISTIOCYTOMA IN FEMALE FISHER RATS BY IMPLANTATION OF CYANOACRYLATE, ZIRCONIA, POLYVINYL CHLORIDE OR SILICONE; IN VIVO 7(2):111-115, 1993]
Species:	RAT
Number of Animals Tested:	(30,28)/(20,19)
Strain/Sex:	SPRAGUE-DAWLEY/MALE
Dose (Inhibitor):	0; 1.5% IN DIET FOR 14 WK BEGINNING 3 D PRIOR TO CARCINOGEN TREATMENT (STUDY DURATION: 26 WK)
Route (Inhibitor):	ORAL
Carcinogen:	1,2-DIMETHYLHYDRAZINE ; 540-73-8
Route (Carcinogen):	SUBCUTANEOUS
Dose (Carcinogen):	20 MG/KG BW 1/WK FOR 12 WK
Promoter:	NONE USED
Target Tissue: Type of Lesion:	INTESTINE: CARCINOMA
Endpoint (Incidence):	23/28 (82%), 14/19 (74%), 10%, NOT SIGNIFICANT
Endpoint (Multiplicity):	1.1, 1.6, -45%, NOT SIGNIFICANT
Comments:	DIFFERENCES IN BODY WEIGHTS BETWEEN GROUPS WERE NOT SIGNIFICANT.
Reference:	[YAMAMOTO,I, MARUYAMA,H AND MORIGUCHI,M; EFFECT OF B-CAROTENE, SODIUM ASCORBATE AND CELLULOSE ON 1,2-DIMETHYLHYDRAZINE-INDUCED INTESTINAL CARCINOGENESIS IN RATS; CANCER LETT. 86(1):5-9, 1994]

As taken from CCRIS powered by Toxnet available at https://toxnet.nlm.nih.gov/newtoxnet/ccris.htm

"Maternal diet during pregnancy has been proposed to modify female offspring's later susceptibility to develop breast cancer; however, most of the dietary factors identified thus far have led to increased risk. To identify dietary factors that might reduce offspring's breast

cancer risk, pregnant rat dams were fed diets containing 6% fiber originating either from cellulose (control), or oat, whole wheat or defatted flax flour. At birth, dams were switched to the AIN93 semi-purified diet. Mammary tumor incidence and multiplicity, induced by administering the offspring 5 mg 7,12-dimethylbenz[a]anthracene (DMBA) at the age of 50 days, was reduced in the whole wheat flour-exposed offspring and increased in the defatted flax-exposed offspring. To identify the mechanisms mediating the effects of in utero dietary exposures, changes in mammary gland morphology and gene expression were assessed before puberty onset (3 weeks of age) and at the time rats are most susceptible to malignant transformation (8 weeks of age). The number of terminal end buds (TEBs), i.e., the targets of malignant transformation, was reduced in the mammary glands of whole wheat- and oat flour-exposed offspring, as compared to the controls. Further, the number of apoptotic epithelial cells (based on ISOL assay) was elevated in the whole wheat flour offspring, but no changes in cell proliferation (PCNA), estrogen receptor alpha (ER-alpha) or cyclin D1 mRNA or protein levels were seen. The mRNA and/or protein levels of BRCA1 and p53 were significantly increased in the mammary glands of whole wheat flour offspring. Further, the levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG), a marker of DNA damage, were significantly reduced in these rats, suggesting that maternal dietary exposure to whole wheat during pregnancy may reduce offspring's breast cancer risk by improving DNA damage repair mechanisms". As taken from Yu B; Khan G; Foxworth A; Huang K; Hilakivi-Clarke L Int J Cancer. 2006, Nov 15; 119(10):2279-86. PubMed, 2009 available at http://www.ncbi.nlm.nih.gov/pubmed/16921499

"A controlled preparation of cellulose nanocrystals of different sizes and shapes has been carried out by acid hydrolysis of microcrystalline cellulose. The size- and concentration-dependent toxicity effects of the resulting cellulose nanocrystals were evaluated against two different cell lines, NIH3T3 murine embryo fibroblasts and HCT116 colon adenocarcinoma. It could serve as a therapeutic platform for cancer treatment." As taken from Hanif Z et al. 2014. Colloids Surf. B Biointerfaces 119, 162-5. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/24856254

"The Panel concluded that microcrystalline cellulose and modified celluloses have no carcinogenic properties and that there was no reason to expect carcinogenic properties with powdered cellulose (E 460(ii))."

As taken from EFSA, 2018

5.7. Irritation/immunotoxicity

SPECIAL STUDIES ON SENSITIZATION

Avicel RCN-15 was determined to be non-sensitizing when topically applied to ten male and ten female Hartley guinea-pigs (Freeman,1991e).

Avicel AC-815 was determined to be non-sensitizing when topically applied to ten male Hartley guinea-pigs (Freeman, 1996c).

SPECIAL STUDIES ON SKIN AND EYE IRRITATION

Avicel RCN-15 was judged to be minimally irritating after instillation into the eyes of four male and two female New Zealand White rabbits (Freeman, 1991c).

Avicel AC-815 was judged to be minimally irritating after instillation into the eyes of four male and two female New Zealand White rabbits (Freeman, 1996a).

Avicel RCN-15 was judged to be non-irritating after a 4-hour occlusive contact with the skin of three male and three female New Zealand White rabbits (Freeman, 1991d).

Avicel AC-815 was judged to be non-irritating after a 4-hour occlusive contact with the skin of three male and three female New Zealand White rabbits (Freeman, 1996b).

As taken from WHO Food Additives Series 40 available at

http://www.inchem.org/documents/jecfa/jecmono/v040je03.htm

“The cytotoxicity and in vitro effects of six variously modified types of cellulose (…… and MCC--microcrystalline cellulose) on the inflammatory response in macrophage-like THP-1 cells were examined, with special focus on their ability to influence gene expression and the production of TNF-α. ….. MCC showed significant anti-inflammatory effects in the LPS-induced conditions, which might be beneficial for the treatment of non-healing chronic wounds, e.g., diabetic or venous ulcers” (Kollar et al. 2011).

“Nanocellulosics are among the most promising innovations for a wide-variety of applications in materials science. Although nanocellulose is presently produced only on a small scale, its possible toxic effects should be investigated at this early stage. The aim of the present study was to examine the potential genotoxicity and immunotoxicity of two celluloses in vitro - cellulose nanocrystals (CNC; mean fibril length 135 nm, mean width 7.3 nm) and a commercially available microcrystalline (non-nanoscale) cellulose (MCC; particle size ~150 µm). ……In human monocyte-derived macrophages, MCC induced a release (measured by enzyme-linked immunosorbent assay; ELISA) of the pro-inflammatory cytokines tumor necrosis factor α (TNF-α) and (after lipopolysaccharide-priming) interleukin 1β (IL-1β) after a 6-h exposure to a dose of 300 µg/ml, but CNC (30-300 µg/ml) did not. In conclusion, our results show that nanosized CNC is neither genotoxic nor immunotoxic under the conditions tested, whereas non-nanosized MCC is able to induce an inflammatory response. More studies are needed, especially in vivo, to further assess if CNC and other nanocelluloses induce secondary genotoxic effects mediated by inflammation.” As taken from Catalán J et al. 2015. Environ. Mol. Mutagen. 56(2), 171-182. PubMed, 2016 available at http://www.ncbi.nlm.nih.gov/pubmed/25257801

“PURPOSE: Neonates are particularly challenging to treat. A novel patented drug delivery device containing a rapidly disintegrating tablet held within a modified nipple shield (NSDS) was designed to deliver medication to infants during breastfeeding. However concerns exist around dermatological nipple tolerability with no pharmaceutical safety assessment guidance to study local tissue tolerance of the nipple and the areola. This is the first Slug Mucosal Irritation (SMI) study to evaluate irritancy potential of GRAS excipients commonly used to manufacture rapidly disintegrating immediate release solid oral dosage form METHODS: Zinc sulphate selected as the antidiarrheal model drug that reduces infant mortality, was blended with functional excipients at traditional levels [microcrystalline cellulose, sodium starch glycolate, croscarmellose sodium, magnesium stearate]. Slugs were exposed to blends slurried in human breast milk to assess their stinging, itching or burning potential, using objective values such as mucus production to categorize irritation potency RESULTS: Presently an in vivo assay, previously validated for prediction of ocular and nasal irritation, was used as an alternative to vertebrate models to anticipate the

potential maternal dermatological tolerability issues to NSDS tablet components. The excipients did not elicit irritancy. However, mild irritancy was observed when zinc sulphate was present in blends. CONCLUSION: These promising good tolerability results support the continued investigation of these excipients within NSDS rapidly disintegrating tablet formulations. Topical local tolerance effects being almost entirely limited to irritation, the slug assay potentially adds to the existing preformulation toolbox, and may sit in between the in vitro and existing in vivo assays." As taken from Kendall R et al. 2017. Pharm. Res. 34(4), 687-695. PubMed, 2018 available at https://www.ncbi.nlm.nih.gov/pubmed/28194635

Basis for ACGIH TWA: upper respiratory tract irritation.

As taken from ACGIH, 2019b

"BACKGROUND: Cellulose is an insoluble plant polysaccharide produced from soft-wood pulp. Although chronic respiratory effects associated with high cellulose-based dust levels have been previously described, occupational asthma has not. A 37 year old machine operator in a sanitary pad production factory presented with new-onset work-related asthma symptoms for two years. METHODS: The worker underwent clinical, pulmonological and immunological (skin prick tests, serum specific IgE determinations) evaluation using standardised procedures. The cellulose product was subjected to scanning electron microscopy (SEM) examination. A specific inhalation challenge test performed with the cellulose product ensured that dust concentrations were kept below 5 mg/m3 . RESULTS: The subject was not atopic and did not have elevated IgE to pine wood or xylanase. The cellulose product appeared to be free of protein contaminants on SEM. The Work Effect Index computed on serial PEF recordings was elevated (WEI = 3.8).Specific inhalational challenge with the cellulose product dust revealed a late bronchial response (39% drop in FEV1 at 3 hours post challenge). CONCLUSION: This is the first reported case of occupational asthma to a cellulose fibre product. A non-specific immune reaction or irritant response seems likely. These fibres may therefore not be biologically inert. The occupational exposure limit of 10 mg/m3 generally used for cellulose dust appears to be non-protective." As taken from Knight D et al. 2018. Am. J. Ind. Med. 61(11). 952-958. PubMed, 2019 available at https://www.ncbi.nlm.nih.gov/pubmed/30232809

5.8. All other relevant types of toxicity

"Intravenous abuse of drugs available in tablet form has led to the detection of excipients, e.g., talc, magnesium stearate or microcrystalline cellulose, in the tissues of a series of 33 fatality cases of intravenous drug addicts. Microcrystalline cellulose (21 cases) and talc (31 cases) were detected most frequently and, in some cases, were associated with granulomatous lesions"

"A double-blind cross-over trial of the effects of guar gum and microcrystalline cellulose on metabolic control and serum lipids in 22 Type 2 diabetic patients has been carried out. The fibre preparations were given at 15 g/day for a 2-week period and then at 5 g/day for the remaining 10-week period of each treatment phase. There was no effect of the microcrystalline cellulose diet on fasting blood glucose level, glycosylated haemoglobin, serum HDL-cholesterol, serum triglycerides, serum zinc or ferritin, or urinary magnesium excretion"

“The effect of various dietary fibres, including microcrystalline cellulose (40 g), on the uptake of vitamin A (approximately sixty times the daily requirement) from a test meal was investigated in 11 female subjects aged 19 to 22. All the dietary fibres significantly increased the absorption of the vitamin A over a period of 9 hours”

“A study of apparent mineral balance in a group of eleven men revealed that there was no significant effect of cellulose, added to the diet at 7.5 g per 1000 kcal for 4 weeks, on the mineral balance of calcium, magnesium, manganese, iron, copper or zinc. However, in this report the source of the cellulose fibre was not specified” “The addition of nutritional grade cellulose (21 g) to the daily diet of healthy adolescent girls resulted in reduction of the serum calcium, phosphorus and iron concentrations. The authors suggested that high-fibre diets may not be advisable” As taken from WHO Food Additives Series 40 available at http://www.inchem.org/documents/jecfa/jecmono/v040je03.htm

CHANGES IN GASTROINTESTINAL FUNCTION AND NUTRIENT BALANCE

“A number of clinical studies using refined cellulose as roughage in the human diet for the treatment of constipation showed no deleterious effects. Groups of 18 children received regular amounts of edible cellulose instead of normal cereal for three months. The only effect noted was an increase in bowel movements but no diarrhoea or other gastrointestinal disturbances were seen (Frey *et al.,* 1928).

Eight male and eight female volunteers supplemented their normal diet with 30 g microcrystalline cellulose per day as either dry powder or gel (15% aqueous) for 6 weeks followed by 2 weeks without supplementation. No adverse findings were reported regarding acceptance or body weight but most subjects complained of fullness and mild constipation. Haematology was normal in all subjects. Biochemical blood values showed no differences between treatment and control periods, nor was there evidence of liver or kidney function disturbance. Urinalysis produced normal findings. The faecal flora remained unchanged. The cellulose content of faeces increase five to eight times during the test period. Microscopy revealed the presence of microcrystalline cellulose (Hazleton Labs, 1962). In another study, eight healthy males received 30 g microcrystalline cellulose daily as supplement to their diet for 15 days. D-xylose absorption varied between pretest, test and post-test periods, being lower during microcrystalline cellulose ingestion. The absorption of 131I-triolein was unaffected by microcrystalline cellulose ingestion. No change was noted in the faecal flora nor was there any significant effect on blood chemistry during ingestion of microcrystalline cellulose. Examination of urine, blood and faecal levels of vitamin B1 during microcrystalline cellulose ingestion showed no difference from control periods (Asahi Chemical Industry Co., 1966).

Twelve men consumed diets containing fibres from various sources for periods of 4 weeks. There was no significant difference between values of serum cholesterol, triglyceride and free fatty acid levels measured after consumption of the basal diet, compared with the values measured after consumption of a diet containing cellulose fibres (90% cellulose, 10% hemicellulose; James River Corp., Berlin, New Hampshire, USA). There were no significant differences in plasma VLDL and HDL cholesterol or in the ratio of

HDL/VLDL+LDL cholesterol. However, the increase in plasma LDL cholesterol after the cellulose diet was significant (Behall *et al.,*1984).

A similar study in a group of four men and six women could detect no effect of a diet containing added alpha-cellulose (15 g daily) on serum total cholesterol, triglycerides, HDL cholesterol and the ratio of HDL to total cholesterol. The cellulose was well tolerated (Hillman *et al.,1*985).

A double-blind cross-over trial of the effects of guar gum and microcrystalline cellulose on metabolic control and serum lipids in 22 Type 2 diabetic patients has been carried out. The fibre preparations were given at 15 g/day for a 2-week period and then at 5 g/day for the remaining 10-week period of each treatment phase. There was no effect of the microcrystalline cellulose diet on fasting blood glucose level, glycosylated haemoglobin, serum HDL-cholesterol, serum triglycerides, serum zinc or ferritin, or urinary magnesium excretion (Niemi *et al.*1988).

The effect of various dietary fibres, including microcrystalline cellulose (40 g), on the uptake of vitamin A (approximately sixty times the daily requirement) from a test meal was investigated in 11 female subjects aged 19 to 22. All the dietary fibres significantly increased the absorption of the vitamin A over a period of 9 hours (Kasper *et al.,* 1979).

A study of apparent mineral balance in a group of eleven men revealed that there was no significant effect of cellulose, added to the diet at 7.5 g per 1000 kcal for 4 weeks, on the mineral balance of calcium, magnesium, manganese, iron, copper or zinc. However, in this report the source of the cellulose fibre was not specified (Behall *et al.,* 1987). The addition of nutritional grade cellulose (21 g) to the daily diet of healthy adolescent girls resulted in reduction of the serum calcium, phosphorus and iron concentrations. The authors suggested that high-fibre diets may not be advisable (Godara *et al.,* 1981).

A study of only three men on a low-fibre diet claimed changes in mineral balance consequent on the consumption of additional cellulose fibre, 10 g of Whatman No. 3 filter paper daily, in the diet (Ismail-Beigi *e al.,*1977).

Microcrystalline cellulose (5 g) did not appear to inhibit the uptake of iron in women who were neither pregnant nor lactating (Gillooly *et al.,*1984).

A group of twenty women, aged 27-48, who were given 20 g packs of alpha-cellulose to be consumed daily for three months, were included in a study of the effect of indole-3-carbinol on estrogen metabolite ratios. Because the control group and the group fed indole-3-carbinol received capsules, the cellulose group could not be blinded; in addition, an unspecified number of subjects in this group dropped out as they found that the cellulose suspension was unpalatable. However, the authors suggest that the estrogen metabolite ratio in the high- fibre group was not different from that in the control group (Bradlow e*t al.,* 1994).”

As taken from WHO Food Additives Series 40 available at http://www.inchem.org/documents/jecfa/jecmono/v040je03.htm

“….Dietary fiber can be separated into many different fractions. These fractions include arabinoxylan, inulin, pectin, bran, cellulose, β-glucan and resistant starch….Dietary fibre components organise functions of large intestine and have important physiological effects on glucose, lipid metabolism and mineral bioavailability. Today, dietary fibers are known to be protective effect against certain gastrointestinal diseases, constipation, hemorrhoids, colon cancer, gastroesophageal reflux disease, duodenal ulcer, diverticulitis, obesity, diabetes, stroke, hypertension and cardiovascular diseases. In this review the physicochemical and biological properties of dietary fibers and their important implications on human health will be investigated.” As taken from Otles S & Ozgoz S. 2014. Acta Sci. Pol. Technol. Aliment. 13(2), 191-202. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/24876314

6. Functional effects on

6.1. Broncho/pulmonary system

“An acute inhalation toxicity study using a preparation of Avicel AC-815 (composed of 85% microcrystalline cellulose and 15% calcium alginate) with mass median aerodynamic diameter of 8.48-8.61 µm (range of measures) was dispersed and delivered at a mean concentration of 5.35 mg/litre in a nose-only inhalation exposure chamber to 5 male and 5 female Crl:CDBR VAF Plus rats for a period of 4 hours. The rats were observed over the 14 days after removal from the chamber. The only signs of toxicity were on removal from the chamber and consisted of chromodacryorrhea, chromorhinorrhea and, in one male rat, decreased locomotion; these signs had resolved by the next day. After 14 days no gross lesions were observed at necropsy” “[…] microcrystalline cellulose has been associated with the formation of granulomas in human lung when it has been injected intravenously during drug abuse. No such lesions have been described as a consequence of oral ingestion of microcrystalline cellulose by rats or humans […]”“In one case intravenous abuse of the drug pentazocine, possibly for longer than six months, led to a fatal pulmonary granulomatosis” As taken from WHO Food Additives Series 40 available at http://www.inchem.org/documents/jecfa/jecmono/v040je03.htm“

Cellulose after single intratracheal dose (15 mg/animal) brought about fibrosing granulomatous alveobronchiolitis and an increase of IgA production in the bronchoalveolar lavage. Fibrosing alveolitis showed moderate progression as a function of time. With different morphological methods, injury of type I pneumocytes and in the incomplete repair of type II pneumocytes were detected. The damage of the alveolar epithelium initiated a series of processes that led to definite pulmonary alterations: pulmonary fibrosis leading to the disintegration of the alveolo-capillary morphological functional unit”. As taken from IUCLID, 2000.

6.2. Cardiovascular system

No data available at this time.

6.3. Nervous system

No data available at this time.

6.4. Other organ systems, dependent on the properties of the substance

“A number of clinical studies using refined cellulose as roughage in the human diet for the treatment of constipation showed no deleterious effects. Groups of 18 children received regular amounts of edible cellulose instead of normal cereal for three months. The only effect noted was an increase in bowel movements but no diarrhoea or other gastrointestinal disturbances were seen” “Eight male and eight female volunteers supplemented their normal diet with 30 g microcrystalline cellulose per day as either dry powder or gel (15% aqueous) for 6 weeks followed by 2 weeks without supplementation. No adverse findings were reported regarding acceptance or body weight but most subjects complained of fullness and mild constipation. Haematology was normal in all subjects. Biochemical blood values showed no differences between treatment and control periods, nor was there evidence of liver or kidney function disturbance. Urinalysis produced normal findings. The faecal flora remained unchanged. The cellulose content of faeces increases five to eight times during the test period. Microscopy revealed the presence of microcrystalline cellulose” As taken from WHO Food Additives Series 40 available at http://www.inchem.org/documents/jecfa/jecmono/v040je03.htm

“….The aim of this study was to clarify the usefulness of microbial cellulose (MC) for use as a dressing and scaffold material. For evaluating the biodegradability and toxicity of MC, we divided the rats (n = 12) into two groups (the implanted group and the non-implanted group). In the implanted group, we implanted the film type of MC in the backs of six rats. In the non-implanted group, however, we did not implant the film type of MC in the backs of the six rats. Four weeks later, we compared two groups by the gross, histological and biochemical characteristics by using blood and tissue samples. To evaluate the wound healing effects of MC, three full-thickness skin defects were made on the backs of each rat (n = 20). Three wounds on the backs of the same rats were treated with other dressing materials, namely, Vaseline gauze (group Con), Algisite M(®) (group Alg) and MC (group MC). We analysed the gross, histological and biochemical characteristics by western blotting. MC was found to be biodegradable and non-toxic. On day 3, the MC film was visible under the subcutaneous tissue; however, after 4 weeks, no remnants of the film were visible under the subcutaneous tissue. Furthermore, there was no evidence of MC-induced toxicity. Moreover, group MC showed more rapid wound healing compared with group Con. On day 14 after skin excision, group MC showed greater decrease in wound size compared with group Con (33% versus 7·2%). The wound healing effects were also substantiated by the histological findings (greater reduction in inflammation and rapid collagen deposition as well as neovascularisation) and western blotting (decreased expression of vascular endothelial growth factor and transforming growth factor-β1 in group MC on day 14 after

skin excision, unlike group Con). This study showed that, in addition to having wound healing effects, MC is biodegradable and non-toxic and can, therefore, be used as a dressing and scaffold material." As taken from Park SU et al. 2014. Int. Wound J. 11(1), 35-43. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/22762434

"The aim of this study was to investigate the therapeutic effects of three different cellulose membranes (CMs) manufactured from Styela clava tunics (SCTs) on the healing of cutaneous wounds. We examined the physical properties and therapeutic effects of three CMs regenerated from SCTs (referred to as SCT-CMs), including normal CM (SCT-CM), freeze-dried SCT-CM (FSCT-CM) and sodium alginate-supplemented SCT-CM (ASCT-CM) on skin regeneration and angiogenesis using Sprague-Dawley (SD) rats. FSCT-CM exhibited an outstanding interlayered structure, a high tensile strength (1.64 MPa), low elongation (28.59%) and a low water vapor transmission rate (WVTR) compared with the other SCT-CMs, although the fluid uptake rate was maintained at a medium level. In the SD rats with surgically wounded skin, the wound area and score of wound edge were lower in the FSCT-CM-treated group than in the gauze (GZ)-treated group on days 3-6 and 12-14. In addition, a significant attenuation in the histopathological changes was observed in the FSCT-CM-treated group. Furthermore, the expression level of collagen-1 and the signaling pathway of transforming growth factor (TGF)-β1 were significantly stimulated by the topical application of FSCT-CM. However, no signs of toxicity were detected in the livers or kidneys of the three SCT-CM-treated groups. Overall, our data indicate that the FSCT-CM may accelerate the process of wound healing in the surgically wounded skin of SD rats through the regulation of angiogenesis and connective tissue formation without inducing any specific toxicity." As taken from Song SH et al. 2017. Int. J. Mol. Med. 39(5), 1173-1187. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/28339010

7. Addiction

JTI is not aware of any information that demonstrates that this ingredient has any addictive effect.

8. Burnt ingredient toxicity

This ingredient was considered as part of an overall safety assessment of ingredients added to tobacco in the manufacture of cigarettes. An expert panel of toxicologists reviewed the open literature and internal toxicology data of 5 tobacco companies to evaluate a composite list of ingredients used in the manufacture of cigarettes. The conclusion of this report was that these ingredients did not increase the inherent biological activity of tobacco cigarettes, and are considered to be acceptable under conditions of intended use (Doull et al., 1994 & 1998).

Tobacco smoke condensates from cigarettes containing cellulose and an additive free, reference cigarettes were tested in a battery of in vitro and/or in vivo test(s). Within the

sensitivity and specificity of the bioassay(s) the activity of the condensate was not changed by the addition of cellulose. Table below provides tested level(s) and specific endpoint(s).

Endpoint	Tested level (ppm)	Reference
Smoke chemistry	70,000 (CAS 65996-61-4)	Baker et al., 2004a
In vitro genotoxicity	28,400 (CAS 65996-61-4)	Baker et al., 2004c
In vitro cytotoxicity	28,400 (CAS 65996-61-4)	Baker et al., 2004c
Inhalation study	28,400 (CAS 65996-61-4)	Baker et al., 2004c

In comparison with a CSC of a reference cigarette with sideseam adhesives/cigarette paper corresponding to representative specifications for the majority of commercial cigarettes no differences were observed either in the bacterial mutagenicity, cytotoxicity or mammalian cell genotoxicity of the smoke condensate prepared from cigarettes with sideseam adhesives/cigarette paper containing Cellulose at 33.3309 mg/cig. The smoke chemistry data between test and reference cigarette revealed small changes towards both higher and lower yields per cigarette over all analytical groups. These differences were well within the variability of the analytical methods (JTI NTM Study Report(s)).

Transfer studies:

“For cellulose in cigarette paper, transfer rates to TPM and gas phase were 9.7% and 20.4% respectively” (Jenkins *et al* 1980).

“Cellulose applied to tobacco blend increased TPM yield and gas phase levels of furan, 2-methylfuran, dimethylfuran, furfuryl alcohol, furfural, 5-methylfurfural, acetaldehyde, propionaldehyde, isobutyraldehyde, crotonaldehyde, acrolein, 2-butanone, 3-butene-2-one, pentadiene and methyl acetate (Wakeham & Silberman 1966).

A casing containing cellulose, glycerol and invert sugar, added to cigarettes made from tobacco sheet, reduced smoke yields of tar, water, nicotine, phenol, acetaldehyde, acrolein, isoprene, hydrogen cyanide, formaldehyde, carbon monoxide, carbon dioxide and catechol. Isoprene, nitrogen oxide, benzo(a)pyrene, indole and neophytadiene yields increased (NCI Report No 4 1980)”.

“Tobacco sheets containing cellulose and other ingredients, reduced cigarette smoke yields of tar, nicotine, carbon monoxide, phenol, polyaromatic hydrocarbons and carbonyl compounds (Prouse *et al* 1977; Briskin 1979; Eicher & Muller 1985). Benzo(a)pyrene yield increased (Dontenwill *et al* 1976)”.

“Adding cellulose to reconstituted tobacco sheet did not increase cigarette smoke condensate bacterial mutagenicity” (Burke 1979).

“Adding cellulose (10%) to cigarettes, did not affect the cytotoxicity or tumourigenicity of smoke condensate, or the ciliatoxicity of smoke (NCI Report No 4 1980)”.

9. Heated/vapor emissions toxicity

No data available to us at this time.

10. Ecotoxicity

10.1. Environmental fate

Photodegradation

Remark: Material is stable.

Source: Celite France SA Nanterre

Stability in Water

Remark: Material is stable

Source: Celite France SA Nanterre

Stability in Soil

Remark: Material is stable

Source: Celite France SA Nanterre

Transport between Environmental Compartments

Remark: inert.

Source: Celite France SA Nanterre

Distribution

Remark: Not considered hazardous for the environment.

Source: Celite France SA Nanterre

Mode of Degradation in Actual Use

Remark: Material is stable

Source: Celite France SA Nanterre

Biodegradation

Remark: Material is stable

Source: Celite France SA Nanterre

BOD5, COD or BOD5/COD Ratio

Remark: Not applicable

Source: Celite France SA Nanterre

As taken from IUCLID Dataset (2000), Cellulose (9004-34-6).

The Ecological Categorization Results from the Canadian Domestic Substances List simply state that cellulose (CAS RN 9004-34-6) is of uncertain persistence in the environment.

Data accessed April 2017 on the OECD website: http://webnet.oecd.org/CCRWeb/Search.aspx

“The degradation kinetics and micro-scale structure change of microcrystalline cellulose during anaerobic biodegradation were investigated. A modified Logistic model was established to properly describe the kinetics, which showed good fitness and wide applicability for cellulose degradation. A maximum degradation rate of 0.14 g L(-1) h(-1) was achieved after cultivating for 51.5 h. This result was in good agreement with the scanning electron microscope and X-ray diffraction analysis. Channels of 400-500 nm size started to occur on the crystalline surface of cellulose at around the inflexion time. Accordingly, the crystallinity significantly decreased at this point, indicating a degradation of the crystalline structure zones by anaerobic bacteria. This study offers direct morphological evidence and quantitative analysis of the biodegradation process of cellulose, and is beneficial to a better understanding of the cellulose degradation mechanism”. As taken from Yu L et al. Chemosphere 86, 348-53. PubMed, 2013 available at http://www.ncbi.nlm.nih.gov/pubmed/22094051?dopt=AbstractPlus

10.2. Aquatic toxicity

Acute/Prolonged Toxicity to Fish

Unit: mg/l

LC50: > 100

Remark: da hochmolkulares

Source: Henkel

Acute Toxicity to Aquatic Invertebrates

Unit: mg/l

EC50: > 100

Remark: da hochmolkulares Polymer

Source: Henkel KGaA Duesseldorf

Toxicity to Aquatic Plants e.g. Algae

Unit: mg/l

EC50: > 100

Remark: da hochmolkulares

Source: Henkel

Toxicity to Microorganisms e.g. Bacteria

Unit: mg/l

EC50: > 100

Remark: da hochmolkulares

Source: Henkel

As taken from IUCLID Dataset (2000), Cellulose (9004-34-6).

Record for cellulose:

Spec. Sci. Name Spec. Common Name	Exp. Type Chem. Anal.	Media Type Loc	Resp. Site Obs. Dur. (Days)	Endpoint BCF	Trend Eff %	Effect Effect Meas.	Conc (Standardized) Appl. Rate	Stat. Signif. Sig. Level
Chlorella vulgaris Green Algae	AQUA - NR U	FW LAB	4		INC 7	POP PGRT	F 50000 ug/L	
Chlorella vulgaris Green Algae	AQUA - NR U	FW LAB	4		INC	PHY PSII	F 50000 ug/L	
Pseudokirchneriella subcapitata Green Algae	AQUA - NR U	FW LAB	4		DEC 1	POP PGRT	F 50000 ug/L	
Pseudokirchneriella subcapitata Green Algae	AQUA - NR U	FW LAB	4		INC	PHY PSII	F 50000 ug/L	

As taken from the EPA ECOTOX database

The Ecological Categorization Results from the Canadian Domestic Substances List simply state that cellulose (CAS RN 9004-34-6) is not inherently toxic to aquatic organisms and is of low ecotoxicological concern.

Data accessed April 2017 on the OECD website: http://webnet.oecd.org/CCRWeb/Search.aspx

“BACKGROUND: MWCNT and CNF [cellulose nanofibers] are interesting NPs that possess great potential for applications in various fields such as water treatment, reinforcement materials and medical devices. However, the rapid dissemination of NPs can impact the environment and in the human health. Thus, the aim of this study was to evaluate the MWCNT and cotton CNF toxicological effects on freshwater green microalgae Chlorella vulgaris. RESULTS: Exposure to MWCNT and cotton CNF led to reductions on algal growth and cell viability. NP exposure induced reactive oxygen species (ROS) production and a decreased of intracellular ATP levels. Addition of NPs further induced ultrastructural cell damage. MWCNTs penetrate the cell membrane and individual MWCNTs are seen in the cytoplasm while no evidence of cotton CNFs was found inside the cells. Cellular uptake of MWCNT was observed in algae cells cultured in BB medium, but cells cultured in Seine river water did not internalize MWCNTs. CONCLUSIONS: Under the conditions tested, such results confirmed that exposure to MWCNTs and to cotton CNFs affects cell viability and algal growth.” As taken from Pereira MM et al. 2014. J. Nanobiotechnology 12, 15. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/24750641

10.3. Sediment toxicity

Remark: No known toxicity

Source: Celite France SA

As taken from IUCLID Dataset (2000), Cellulose (9004-34-6).

10.4. Terrestrial toxicity

Remark: No known toxicity

Source: Celite France SA

As taken from IUCLID Dataset (2000), Cellulose (9004-34-6).

10.5. All other relevant types of ecotoxicity

Remark: No known toxicity

Source: Celite France SA

Bioaccumulation

Remark: Not applicable

Source: Celite France SA

As taken from IUCLID Dataset (2000), Cellulose (9004-34-6).

The Ecological Categorization Results from the Canadian Domestic Substances List simply state that cellulose (CAS RN 9004-34-6) is of uncertain bioaccumulative potential in the environment.

Data accessed April 2017 on the OECD website: http://webnet.oecd.org/CCRWeb/Search.aspx

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13. Last audited

October 2019

Toxicological profile for

Cellulose

This ingredient has been assessed to determine potential human health effects for the consumer. It was considered not to increase the inherent toxicity of the product and thus is acceptable under conditions of intended use.

1. Name of substance and physico-chemical properties

1.1. IUPAC systematic name

(2S,3R,4S,5S,6R)-2-[(2R,3S,4R,5R,6S)-4,5-Dihydroxy-2-(hydroxymethyl)-6-[(2R,3S,4R,5R,6R)-4,5,6-trihydroxy-2-(hydroxymethyl)oxan-3-yl]oxyoxan-3-yl]oxy-6-(hydroxymethyl)oxane-3,4,5-triol (PubChem)

1.2. Synonyms

Rayon; Rayon, purified; UNII-BX81F82EWG; Viscose fiber (ChemIDplus); d-Cellotriose; Cellulose, regenerated; regenerated cellulose; beta-cellotriose; Cellulase; beta-D-Glucopyranosyl-(1->4)-beta-D-glucopyranosyl-(1->4)-beta-D-glucopyranose (PubChem)

1.3. Molecular formula

Unspecified (ChemIDplus); $C_{18}H_{32}O_{16}$ (PubChem)

1.4. Structural Formula

(ChemIDplus)

1.5. Molecular weight (g/mol)

504.4348 (ChemIDplus)

1.6. CAS registration number

61788-77-0

1.7. Properties

1.7.1. Melting point

(°C): 349-84 (estimated) (EPISuite, 2017)

1.7.2. Boiling point

(°C): 802.65 (estimated) (EPISuite, 2017)

1.7.3. Solubility

1e+006 mg/L at 25°C (estimated) (EPISuite, 2017)

1.7.4. pKa

No data available to us at this time.

1.7.5. Flashpoint

(°C): No data available to us at this time.

1.7.6. Flammability limits (vol/vol%)

No data available to us at this time.

1.7.7. (Auto)ignition temperature

(°C): No data available to us at this time.

1.7.8. Decomposition temperature

(°C): No data available to us at this time.

1.7.9. Stability

No data available to us at this time.

1.7.10. Vapor pressure

1.46E-025 mmHg at 25°C (estimated) (EPISuite, 2017)

1.7.11. log Kow

-7.36 (estimated) (EPISuite, 2017); -6.9 (estimated) (PubChem)

2. General information

2.1. Exposure

INCI Name	RAYON
Description	Cellulose, regenerated. The product is obtained by treating cellulose with caustic soda, reacting this with carbon disulfide, dissolving this in a dilute alkali solution and extruding into an acid to form a continuous viscose tube
INN Name	
Ph. Eur. Name	
CAS #	68442-85-3 / 61788-77-0
EINECS/ELINCS #	270-493-7 / -
Chemical/IUPAC Name	

Cosmetic Restriction	
Other Restriction(s)	
Functions	BULKING VISCOSITY CONTROLLING
SCCS opinions	
Identified INGREDIENTS or substances e.g.	

As taken from CosIng (Cosmetic substances and ingredients database). Accessed August 2019, available at http://ec.europa.eu/growth/tools-databases/cosing/

National Occupational Exposure Survey (1981 - 1983)

Estimated Numbers of Employees Potentially Exposed to Specific Agents by Occupation*

Agent Name	RAYON (MF UNKNOWN)		
CAS #	61788-77-0		
RTECS #			
Agent Code	X6471		
Code	Occupation Description (1980)	Total # Employees (Male & Female)	Total # Female Employees
449	MAIDS AND HOUSEMEN	2,367	1,288
TOTAL		2,367	1,288

*(1) The estimates for each occupation apply across the surveyed industries in which the agent was observed. Not all industries were surveyed, and not all agents were observed in all surveyed industries. (2) When using the estimates, standard errors associated with estimates should be considered. (3) Potential exposures to a chemical agent are categorized as actual (i.e., the surveyor observed the use of the specific agent) or tradename (i.e., the surveyor observed the use of a tradename product known to contain the specific agent). The estimates presented in the table combine both categories.

As taken from NIOSH, available at https://web.archive.org/web/20111028122746/http://www.cdc.gov/noes/noes2/x6471occ.html

2.2. Combustion products

This ingredient was investigated in a pyrolysis study. Results are given in JTI Study Report (s).

Compound	Two stage heating		One stage heating	
	Abundance	Area%	Abundance	Area%
acetone	17205988	1.06	8355698	0.57
acetic acid	256330301	1.58	23513104	1.60
acetol	34103603	2.10	24177932	1.65
2-cyclopenten-1-one + unknown	34670406	2.14	22937462	1.56
furfural	47125884	2.90	56584048	3.86
1,2-cyclopentanedione	18899160	1.16	12472713	0.85
3-methyl-2,5-furandione + unknown	26846932	1.65	23115994	1.58
2H-pyran-2,6(3H)-dione	29606121	1.82	21465379	1.46
2-furancarboxylic acid	23045299	1.42	20692827	1.41
3,5-dihydroxy-2-methyl-4H-pyran-4-one	18322628	1.13	20068994	1.37
unknown	42470578	2.62	37686848	2.57
1,4:3,6-dianhydro-alpha-D-glucopyranose	23637096	1.46	20544754	1.40
5-hydroxymethylfurfural	78400335	4.83	81445343	5.55
unknown	17834203	1.10	10476614	0.71
unknown	17213131	1.06	12222776	0.83
unknown	57099159	3.52	44673662	3.05
levoglucosan	561411098	34.57	625527613	42.64

1,6-anhydro-beta-D-glucofuranose	40779397	2.51	34278165	2.34
Total ion chromatogram	**1624677171**	**100**	**1464878846**	**100**

“A rapid, semi-micropyrolysis technique was developed and applied to materials representative of tobacco cell-wall constituents and sucrose. Glass capillary gas chromatography - mass spectrometry was used to separate and identify the major semi-volatile pyrolyzate components. Cellulose and dextrin produced a pattern of furan and cyclic ketones of potential importance to flavour and aroma of tobacco smoke. Sucrose pyrolysis resulted in the formation of substantial amounts of 2-furaldehyde and lesser quantities of substituted furans. The cell-wall biopolymer lignin was a source of phenols, but contributed little to the compounds produced in the thermal breakdown of carbohydrates.” As taken from Schlotzhauer WS et al. 1985. Beiträge zur Tabakforschung 13(2), 74-80. Available at: http://www.degruyter.com/view/j/cttr.1985.13.issue-2/cttr-2013-0558/cttr-2013-0558.xml?rskey=fluZed&result=17

Table 1.
Identified pyrolyzate components.

Peak No.	Compound	Molecular weight	Formula	Percentage of total volatiles from chromatograms of pyrolyzates of			
				cellulose	dextrin	sucrose	lignin
1	2-Methylfuran	82	C_5H_6O	0.3			
2	3-Methylfuran	82	C_5H_6O	6.1	19.9	3.0	
3	2-Methyl-2-cyclopenten-1-one	96	C_6H_8O		2.0	0.3	
4	Propionic acid methyl ester	88	$C_4H_8O_2$	1.1	2.5	0.6	
5	2,4-Pentanedione	100	$C_5H_8O_2$		1.8	0.4	
6	2-Methyl-2-pentenal	98	$C_6H_{10}O$		1.1		
7	5-Methyl-3-hydrofuran-2-one	98	$C_5H_6O_2$			0.6	
8	2-Furaldehyde	96	$C_5H_4O_2$	20.7	16.7	67.1	
9	2-Acetylfuran	110	$C_6H_6O_2$	0.8		0.7	
10	5-Methyl-2-furaldehyde	110	$C_6H_6O_2$	2.1	1.7	4.2	
11	3,5,5-Trimethyl-2-cyclopenten-1-one	124	$C_8H_{12}O$	0.7	0.6	0.5	
12	Dihydro-2(3*H*)-furanone	86	$C_4H_6O_2$			0.7	
13	2,3,4-Trimethyl-2-cyclopenten-1-one	124	$C_8H_{12}O$		1.1	0.9	
14	2-Furanmethanol	98	$C_5H_6O_2$	2.0	3.8	2.4	0.9
15	5-Methyl-2(5*H*)-furanone	98	$C_5H_6O_2$	0.9	1.1		
16	3-Methyl-2(5*H*)-furanone	98	$C_5H_6O_2$	0.7	0.9		
17	3-Hydroxybenzaldehyde	122	$C_7H_6O_2$			0.1	
18	Cyclopentanone	84	C_5H_8O	2.5	2.8	0.5	
19	2-Pyrone	96	$C_5H_4O_2$			0.6	
20	1,3-Cyclopentanedione	98	$C_5H_6O_2$	3.6	6.2	1.6	
21	4*H*-Pyran-4-one	96	$C_5H_4O_2$		1.5		
22	2-Hydroxy-3-methyl-2-cyclopenten-1-one	112	$C_6H_8O_2$	2.3	2.1	0.5	1.8
23	3-Methyl-2,4(3*H*,5*H*)-furandione	114	$C_5H_6O_3$	5.1			
24	3-Hydroxy-2-methylpyran-4-one	126	$C_6H_6O_3$	10.0	1.1		
25	1,4-Dimethoxybenzene	138	$C_8H_{10}O_2$				1.3
26	a Furancarboxylic acid methyl ester	126	$C_6H_6O_3$	6.9	1.4	2.0	
27	Phenol + *o*-cresol	94 + 108	$C_6H_6O + C_7H_8O$	0.9	1.3	0.7	12.3
28	*m*-Cresol + *p*-cresol	108	C_7H_8O	0.7	0.5	0.5	16.6
29	4-Ethylphenol	122	$C_8H_{10}O$				2.6
30	2-Ethyl-5-methylphenol	136	$C_9H_{12}O$				1.3
31	an Ethyl dimethyl phenol	150	$C_{10}H_{14}O$				0.6
32	3,4-Dimethoxyphenol	154	$C_8H_{10}O$				0.7

As taken from Schlotzhauer WS et al. 1985. Beiträge zur Tabakforschung 13(2), 74-80. Available at: http://www.degruyter.com/view/j/cttr.1985.13.issue-2/cttr-2013-0558/cttr-2013-0558.xml?rskey=fIuZed&result=17

2.3. Ingredient(s) from which it originates

Cellulose (CAS RN not given) is found in stem bark from ambrette, dry stems of genet, kola nut, tragacanth (1-4%) and luffa sponge.

As taken from Khan and Abourashed, 2010

Cellulose, regenerated. The product is obtained by treating cellulose with caustic soda, reacting this with carbon disulfide, dissolving this in a dilute alkali solution and extruding into an acid to form a continuous viscose tube.

As taken from CosIng (Cosmetic substances and ingredients database). Accessed August 2019, available at http://ec.europa.eu/growth/tools-databases/cosing/

“Rayon is a manufactured regenerated cellulose fiber. It is made from purified cellulose, primarily from wood pulp, which is chemically converted into a soluble compound. It is then dissolved and forced through a spinneret to produce filaments which are chemically solidified, resulting in synthetic fibers of nearly pure cellulose.”

As taken from Haz-Map, 2018

3. Status in legislation and other official guidance

FDA 21 CFR 176.170 - INDIRECT FOOD ADDITIVES: PAPER AND PAPERBOARD COMPONENTS. SUBSTANCES FOR USE ONLY AS COMPONENTS OF PAPER AND PAPERBOARD. Components of paper and paperboard in contact with aqueous and fatty foods.

FDA 21 CFR 177.2260 - INDIRECT FOOD ADDITIVES: POLYMERS. SUBSTANCES FOR USE ONLY AS COMPONENTS OF ARTICLES INTENDED FOR REPEATED USE. Filters, resin-bonded.

FDA 21 CFR 177.2800 - INDIRECT FOOD ADDITIVES: POLYMERS. SUBSTANCES FOR USE ONLY AS COMPONENTS OF ARTICLES INTENDED FOR REPEATED USE. Textiles and textile fibers.

As taken from FDA (2018; 2019)

Pre-registered under REACH (“envisaged registration deadline 31 May 2018”) (ECHA, 2018).

Rayon (CAS RN 61788-77-0) is listed in the US EPA InertFinder Database (2019) as approved for non-food use pesticide products.

Rayon (CAS RN 61788-77-0) is included on the New Zealand Inventory of Chemicals and may be used as a component in a product covered by a group standard but it is not approved for use as a chemical in its own right (NZ EPA, 2006).

Rayon (CAS RN 61788-77-0) is “not considered to pose an unreasonable risk to the health of workers and public health on the basis of the Tier I IMAP assessment” by the Australian Government Department of Health (NICNAS, 2018).

4. Metabolism/Pharmacokinetics

4.1. Metabolism/metabolites

No data available to us at this time.

4.2. Absorption, distribution and excretion

No data available to us at this time.

4.3. Interactions

No data available to us at this time.

5. Toxicity

5.1. Single dose toxicity

No data available to us at this time.

5.2. Repeated dose toxicity

No data available to us at this time.

5.3. Reproduction toxicity

No data available to us at this time.

5.4. Mutagenicity

No data available to us at this time.

5.5. Cytotoxicity

No data available to us at this time.

5.6. Carcinogenicity

In a case–controlled study in 556 women with malignant breast cancer, the odds ratio doubled or more for each 10-year increase in exposure to rayon fibres for oestrogen-positive and progesterone-negative tumours (LaBreche et al. 2010).

5.7. Irritation/immunotoxicity

No data available to us at this time.

5.8. All other relevant types of toxicity

No data available to us at this time.

6. Functional effects on

6.1. Broncho/pulmonary system

“Background: Following employee respiratory concerns, we investigated the health effects of rayon flock exposure at a card manufacturing plant. METHODS: We conducted a cross-sectional survey including environmental evaluation, standardized questionnaires, spirometry, carbon monoxide diffusing capacity testing, and methacholine challenge testing. RESULTS: From a total of 239 participants, 146 (61%) reported working at least 1 hr per week in areas where flock-coated cards are processed (flock workers) and 47 (20%) reported cleaning equipment with compressed air. These workers had generally higher prevalences of respiratory symptoms. Flock workers and employees with longer tenure at areas where flock-coated cards are processed were more likely to have restrictive impairment of lung function. Although dust and fiber samples were largely below the detection limits, peak exposures to airborne particulate occurred during cleaning with compressed air. CONCLUSIONS: Working with rayon flock and cleaning with compressed air were associated with health effects in workers at this plant” (Antao et al. 2007).

6.2. Cardiovascular system

No data available to us at this time.

6.3. Nervous system

No data available to us at this time.

6.4. Other organ systems, dependent on the properties of the substance

No data available to us at this time.

7. Addiction

JTI is not aware of any information that demonstrates that this ingredient has any addictive effect.

8. Burnt ingredient toxicity

This ingredient was considered as part of an overall safety assessment of ingredients added to tobacco in the manufacture of cigarettes. An expert panel of toxicologists reviewed the open literature and internal toxicology data of 5 tobacco companies to evaluate a composite list of ingredients used in the manufacture of cigarettes. The conclusion of this report was that these ingredients did not increase the inherent biological activity of tobacco cigarettes, and are considered to be acceptable under conditions of intended use (Doull et al., 1994 & 1998).

9. Heated/vapor emissions toxicity

No data available to us at this time.

10. Ecotoxicity

10.1. Environmental fate

No data available to us at this time.

10.2. Aquatic toxicity

No data available to us at this time.

10.3. Sediment toxicity

No data available to us at this time.

10.4. Terrestrial toxicity

No data available to us at this time.

10.5. All other relevant types of ecotoxicity

No data available to us at this time.

11. References for conventional products

- Antao VCS et al. (2007). Rayon flock: a new cause of respiratory morbidity in a card processing plant. American Journal of Industrial Medicine, 50, 274-284. Abstract available via PubMed at http://www.ncbi.nlm.nih.gov/pubmed/17370318
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- ECHA (2018). European Chemicals Agency. Information on Chemicals. Record for rayon. Last updated 7 February 2018. Available at: https://echa.europa.eu/information-on-chemicals/pre-registered-substances
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https://www.epa.gov/tsca-screening-tools/download-epi-suitetm-estimation-program-interface-v411

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- Labreche F, Goldberg MS, Valois M-F and Nadon L (2010). Postmenopausal breast cancer and occupational exposures. Occupational and Environmental Medicine 67, 263-269
- NICNAS (2018). Australian Government Department of Health. National Industrial Chemicals Notification and Assessment Scheme. Inventory Multi-Tiered Assessment and Prioritisation (IMAP) Framework. Tier I Human Health Assessments. Last updated 29 July 2018. Accessed August 2019. Available at: https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessments/human-health-assessments
- NIOSH. National Institute for Occupational Safety and Health. National Occupational Exposure Survey (1981-1983). Available at https://web.archive.org/web/20111028131052/http://www.cdc.gov/noes/noes2/x6471occ.html
- NZ EPA (2006). New Zealand Environmental Protection Authority. Inventory of Chemicals. Record for rayon (CAS RN 61788-77-0). Date added to inventory: 1 December 2006. Accessed August 2019. Available at: https://www.epa.govt.nz/database-search/new-zealand-inventory-of-chemicals-nzioc/view/30830
- PubChem (2019). Record for cellulase (CAS RN 61788-77-0). Created 24 June 2005. Last modified 1 August 2019. Available at https://pubchem.ncbi.nlm.nih.gov/compound/440950
- Schlotzhauer WS et al. (1985). The Rapid Pyrolytic Characterization of Tobacco Leaf Carbohydrate Material. Beiträge zur Tabakforschung 13(2), 74-80. Available at: http://www.degruyter.com/view/j/cttr.1985.13.issue-2/cttr-2013-0558/cttr-2013-0558.xml?rskey=fIuZed&result=17
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12. Other information

- Paschke T et al. (2002). Effects of Ingredients on Cigarette Smoke Composition and Biological Activity: A Literature Overview. Beiträge zur Tabakforschung 20(3), 107-247. Available at: http://www.degruyter.com/view/j/cttr.2002.20.issue-3/cttr-2013-0736/cttr-2013-0736.xml?rskey=fIuZed&result=13
- Rodgman A (2004). Some Studies of the Effects of Additives on Cigarette Mainstream Smoke Properties. III. Ingredients Reportedly Used in Various Commercial Cigarette Products in the USA and Elsewhere. Beiträge zur Tabakforschung 21(2), 47–104. Available at: http://www.degruyter.com/view/j/cttr.2004.21.issue-2/cttr-2013-0771/cttr-2013-0771.xml?rskey=B9UDrP&result=2

13. Last audited

September 2019

Toxicological profile for

Cellulose

This ingredient has been assessed to determine potential human health effects for the consumer. It was considered not to increase the inherent toxicity of the product and thus is acceptable under conditions of intended use.

1. Name of substance and physico-chemical properties

1.1. IUPAC systematic name

No data available to us at this time.

1.2. Synonyms

Bleached ground wood pulp; Cellulose chemical pulp; Cellulose cotton linter pulp; Cellulose, chemical pulp; Chemical pulp, non-sulfur; EINECS 265-995-8; Pulp, cellulose; Rags; Cellulose, pulp (ChemIDplus)

1.3. Molecular formula

(C6 H10 O5)x

1.4. Structural Formula

No data available to us at this time.

1.5. Molecular weight (g/mol)

160,000-560,000

1.6. CAS registration number

65996-61-4

1.7. Properties

1.7.1. Melting point

(°C): 500

1.7.2. Boiling point

(°C): Decomposes.

1.7.3. Solubility

Practically insoluble in water.

1.7.4. pKa

pH 5.0 (100 g/l, H2O, 20ºC)

1.7.5. Flashpoint

(°C): No data available to us at this time.

1.7.6. Flammability limits (vol/vol%)

No data available to us at this time.

1.7.7. (Auto)ignition temperature

(°C): No data available to us at this time.

1.7.8. Decomposition temperature

(°C): No data available to us at this time.

1.7.9. Stability

Stable at normal temperatures and pressure.

1.7.10. Vapor pressure

Not applicable.

1.7.11. log Kow

No data available to us at this time.

2. General information

2.1. Exposure

Cellulose (CAS RN 65996-61-4) is listed as an ingredient in home maintenance, inside the home, personal care and pet care products by the US Department of Health and Human Services (2018).

National Occupational Exposure Survey (1981 - 1983)

Estimated Numbers of Employees Potentially Exposed to Pulp, Cellulose (CAS RN 65996-61-4) by Occupation*

Code	Occupation Description (1980)	Total # Employees (Male & Female)	Total # Female Employees
095	REGISTERED NURSES	1,483	1,448
364	TRAFFIC, SHIPPING, AND RECEIVING CLERKS	3,254	
453	JANITORS AND CLEANERS	535	50
567	CARPENTERS	14	
593	INSULATION WORKERS	98	
633	SUPERVISORS, PRODUCTION OCCUPATIONS	354	
675	HAND MOLDERS AND SHAPERS, EXCEPT JEWELERS	232	
696	STATIONARY ENGINEERS	140	59
709	GRINDING, ABRADING, BUFFING, AND POLISHING MACHINE OPERATORS	324	17
717	FABRICATING MACHINE OPERATORS, N.E.C.	118	59
719	MOLDING AND CASTING MACHINE OPERATORS	3,375	832

734	PRINTING MACHINE OPERATORS	753	
736	TYPESETTERS AND COMPOSITORS	1,069	950
737	MISCELLANEOUS PRINTING MACHINE OPERATORS	1,283	837
744	TEXTILE SEWING MACHINE OPERATORS	2,841	1,484
749	MISCELLANEOUS TEXTILE MACHINE OPERATORS	1,661	
753	CEMENTING AND GLUING MACHINE OPERATORS	203	
756	MIXING AND BLENDING MACHINE OPERATORS	163	
765	FOLDING MACHINE OPERATORS	769	710
766	FURNACE, KILN, AND OVEN OPERATORS, EXC. FOOD	66	47
769	SLICING AND CUTTING MACHINE OPERATORS	548	29
777	MISCELLANEOUS MACHINE OPERATORS, N.E.C.	3,033	98
779	MACHINE OPERATORS, NOT SPECIFIED	1,218	192
785	ASSEMBLERS	1,748	594
796	PRODUCTION INSPECTORS, CHECKERS, AND EXAMINERS	192	
804	TRUCK DRIVERS, HEAVY	152	
856	INDUSTRIAL TRUCK AND TRACTOR EQUIPMENT OPERATORS	405	
859	MISCELLANEOUS MATERIAL MOVING EQUIPMENT OPERATORS	17	
888	HAND PACKERS AND PACKAGERS	445	107
TOTAL		26,494	7,513

*(1) The estimates for each occupation apply across the surveyed industries in which the agent was observed. Not all industries were surveyed, and not all agents were observed in all surveyed industries. (2) When using the estimates, standard errors associated with estimates should be considered. (3) Potential exposures to a chemical agent are categorized as actual (i.e., the surveyor observed the use of the specific agent) or tradename (i.e., the surveyor observed the use of a tradename product known to contain the specific agent). The estimates presented in the table combine both categories.

As taken from NIOSH, available at https://web.archive.org/web/20111028122746/http://www.cdc.gov/noes/noes2/x1140occ.html

2.2. Combustion products

This ingredient was investigated in a pyrolysis study. Results are given in JTI Study Report (s).

Compound	Two stage heating		One stage heating	
	Abundance	Area%	Abundance	Area%
acetone	17205988	1.06	8355698	0.57
acetic acid	256330301	1.58	23513104	1.60
acetol	34103603	2.10	24177932	1.65
2-cyclopenten-1-one + unknown	34670406	2.14	22937462	1.56
furfural	47125884	2.90	56584048	3.86
1,2-cyclopentanedione	18899160	1.16	12472713	0.85
3-methyl-2,5-furandione + unknown	26846932	1.65	23115994	1.58
2H-pyran-2,6(3H)-dione	29606121	1.82	21465379	1.46
2-furancarboxylic acid	23045299	1.42	20692827	1.41
3,5-dihydroxy-2-methyl-4H-pyran-4-one	18322628	1.13	20068994	1.37

unknown	42470578	2.62	37686848	2.57
1,4:3,6-dianhydro-alpha-D-glucopyranose	23637096	1.46	20544754	1.40
5-hydroxymethylfurfural	78400335	4.83	81445343	5.55
unknown	17834203	1.10	10476614	0.71
unknown	17213131	1.06	12222776	0.83
unknown	57099159	3.52	44673662	3.05
levoglucosan	561411098	34.57	625527613	42.64
1,6-anhydro-beta-D-glucofuranose	40779397	2.51	34278165	2.34
Total ion chromatogram	1624677171	100	1464878846	100

This ingredient was investigated in a pyrolysis study. Results are given in Baker and Bishop (2005) J. Anal. Appl. Pyrolysis 74, 145–170.

Ingredient Name & CAS Number	Max. cig. appln. level (ppm)	Composition of pyrolysate (Compound, %)		Max. level in smoke (µg)
Cellulose fiber 65996-61-4	17000	Hydroymethylfurfural	9.9	840 650 540 410 370 260 220 180
		Acetol	7.6	
		Methyl formate? and/or hydroxyacetaldehyde	6.3	
		Furfural	4.8	
		Methyl pyruvate	4.3	
		Benzene	3.1	
		Acetic acid + 2-butenal	2.6	
		Phenol + methylfuranone+ethyltoluene	2.1	

Cellulose has been pyrolysed many different ways. The pyrolysis products were phenol; pyrogallol; m-cresol; o-cresol; p-cresol; formaldehyde; acetaldehyde; propionaldehyde; n-butyraldehyde; 2-furaldehyde; 5-hydroxymethylfuraldehyde; 5-methyl-2-furaldehyde; acetone; methyl ethyl ketone; acrolein; 2-buten-3-one; 3-hydroxy-2-methylpyran-4-one; 3-methyl-2, 4-(3H, 5H)-furandione; 1,3-cyclopentanedione; glucopyranose; picene; benzo(a)pyrene; fluoranthrene; anthracene; 4, 5-methylenphenanthrene; phenanthrenequinone; anthraquinone; pyrenequinone; furfural; 5-hydroxymethylfurfural; furancarboxylic acid methyl ester; propionic acid methyl ester; 3-methylfuran; methanol; 2-furanmethanol; glyoxal; formic acid; acetic acid; lactic acid; carbon monoxide; carbon dioxide; water; levoglucosan (Bell *et al* 1966; Schlotzhauer *et al* 1967 & 1985; Sakuma *et al* 1981; Kroller 1964a; Lewin & Basch 1978).

Cellulose Pyrolysate contained more benzopyrene than tobacco pyrolysate (Gilbert & Lindsay 1957; Robb *et al* 1966).

Pyrolysis of cellulose yields a greater percentage of low molecular weight ketones and aldehydes, such as acetaldehyde and hydroxyacetaldehyde, relative to glucose, fructose and sucrose (Sanders et al. 2003).

2.3. Ingredient(s) from which it originates

21 CFR Section 186.1673: “Pulp is the soft, spongy pith inside the stem of a plant such as wood, straw, sugarcane, or other natural plant sources.”

As taken from FDA, 2019a

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

As taken from ChemIDplus.

3. Status in legislation and other official guidance

The EU Scientific Committee on Food has placed cellulose in List 0, as a compound that can be used in food-contact materials without the need for establishing an ADI figure (Commission 2002).

High production volume (HPV) chemical; in excess of 1 million pounds produced in US annually (Scorecard).

Approved under 21 CFR 177.1460 (indirect food additives: polymers; melamine-formaldehyde resins in molded articles), 177.1900 (indirect food additives: polymers; urea-formaldehyde resins in molded articles) and 177.2260 (indirect food additives: polymers; filters, resin-bonded). As taken from FDA, 2018, 2019.

Approved under 21 CFR 186.1673 (Indirect food substances affirmed as generally recognized as safe. Pulp). As taken from FDA, 2019.

Pulp, cellulose is pre-registered under REACH ("envisaged registration deadline 30 November 2010") (ECHA, 2018).

Pulp, cellulose (CAS RN 65996-61-4) is not classified for packaging and labelling under Regulation (EC) No. 1272/2008 (ECHA, 2019).

Pulp, cellulose (CAS RN 65996-61-4) is included on the Safer Chemical Ingredients list (US EPA, 2019).

Rags (CAS RN 65996-61-4) is listed in the US EPA Toxic Substances Control Act (TSCA) inventory, and also in the US EPA 2012 CDR and 2016 CDR Full Exempt lists (Chemical Data Reporting Rule). The Chemical Data Reporting (CDR) Rule requires companies that manufacture (including import) certain chemicals at certain volumes in the U.S. to report to EPA every four years through its CDR.

The TSCA inventory, and 2012 CDR and 2016 CDR Full Exempt lists are available at https://iaspub.epa.gov/sor_internet/registry/substreg/searchandretrieve/searchbylist/search.do

Pulp, cellulose is a "chemical identified as low concern to human health by application of expert validated rules" according to the Tier I IMAP assessment conducted by the Australian Department of Health (NICNAS, 2019).

Pulp, cellulose (CAS RN 65996-61-4) is included on the New Zealand Inventory of Chemicals and may be used as a component in a product covered by a group standard but it is not approved for use as a chemical in its own right (NZ EPA, 2006).

4. Metabolism/Pharmacokinetics

4.1. Metabolism/metabolites

"A double-blind cross-over trial of the effects of guar gum and microcrystalline cellulose on metabolic control and serum lipids in 22 Type 2 diabetic patients has been carried out. The

fibre preparations were given at 15 g/day for a 2-week period and then at 5 g/day for the remaining 10-week period of each treatment phase. There was no effect of the microcrystalline cellulose diet on fasting blood glucose level, glycosylated haemoglobin, serum HDL-cholesterol, serum triglycerides, serum zinc or ferritin, or urinary magnesium excretion" As taken from WHO Food Additives Series 40 available at http://www.inchem.org/documents/jecfa/jecmono/v040je03.htm

4.2. Absorption, distribution and excretion

"Groups of male and female Sprague-Dawley CD rats (20 per group) from Charles River Laboratories were administered, by gavage, suspensions of a special fine particle-size microcrystalline cellulose (median particle size 6 µm). The rats were dosed orally daily for 90 consecutive days at a level of 5000 mg/kg bw per day by means of a 25% suspension in tap water. The animals were killed on study days 91-94 and necropsies were carried out under conditions that reduced the possibility of contamination of tissues with fine particulates. The birefringent microcrystalline cellulose particles were not detected in any organ or tissue, including gut-associated lymphoid tissue, liver, lung, spleen and brain."

"In another study, dyed plant foods (oatmeal, creamed corn) were fed to human subjects, and blood and urine were examined for coloured fibres. Dyed fibres were shown to be present (Schreiber, 1974). Lycopodium spores and pollen grains have also been shown to be persorbed by humans."

"Rats, pigs and dogs were used to study the persorption of microcrystalline cellulose. The animals were not fed for 12 hours prior to oral administration of the test compound. Rats, dogs and pigs were given 0.5, 140 and 200 g, respectively, of the test compound. Venous blood was taken from the animals 1-2 hours after administration of the test compound, and examined for particles. Persorbed particles were demonstrated in the blood of all three species. The average maximum diameter for persorbed particles was greater in rats than in dogs or pigs."

"In another study, eight healthy males received 30 g microcrystalline cellulose daily as supplement to their diet for 15 days. D-xylose absorption varied between pretest, test and post-test periods, being lower during microcrystalline cellulose ingestion. The absorption of 131I-triolein was unaffected by microcrystalline cellulose ingestion. No change was noted in the faecal flora nor was there any significant effect on blood chemistry during ingestion of microcrystalline cellulose. Examination of urine, blood and faecal levels of vitamin B1 during microcrystalline cellulose ingestion showed no difference from control periods."

"Four rats were fed 14C-labelled microcrystalline cellulose at 10 or 20% of their diet. No evidence of degradation or digestion was noted. Faecal recoveries of radioactivity ranged from 96-104% and were complete for all labelled material. No radioactivity appeared in the urine"

“One human subject received 150 g of microcrystalline cellulose daily in two portions for a 15-day adaptation period. He then received 14C-labelled microcrystalline cellulose (47.6 µCi) in two portions on one day. Supplementation of the diet with unlabelled microcrystalline cellulose continued for 10 days. Twenty-four-hour faecal and urine collections were examined for radioactivity. No radioactivity appeared in the urine or in the expired CO2. All administered radioactivity (98.9 ± 3.0%) was recovered from the faeces within two days.”

“Most (87%) of the radiolabel associated with 131I-labelled alpha-cellulose fibres (retained by a sieve with pores of 1 mm diam) was excreted by 4 male and 4 female volunteers within 5 days of ingestion. Less than 2% of the faecal radiolabel was unbound; urinary excretion of unbound radio-iodine accounted for another 1.9% of the total dose.” As taken from WHO Food Additives Series 40 available at http://www.inchem.org/documents/jecfa/jecmono/v040je03.htm

4.3. Interactions

No data available to us at this time.

5. Toxicity

5.1. Single dose toxicity

Species	Sex	Route	LD_{50} (g/kg bw)
Rat	M	Oral	>3.16
Rat	M+F	Oral	>5.00
Rat	M+F	Oral	>5.00
Rat	M	Intraperitoneal	>3.16
Rat	M+F	Dermal	>2.00
Rat	M+F	Dermal	>2.00
Rat	M+F	Dermal	>2.00
Rat	M+F	Inhalation	>5.35-5.8

“[…] there was no evidence of toxicity of microcrystalline cellulose preparations administered either orally or dermally to rats at doses of 5000 or 2000 mg/kg bw,

respectively. The observations seen at necropsy in animals treated intraperitoneally with Cellan 300 at 3160 mg/kg bw are consistent with an irritant reaction caused by the presence of foreign material. An inhalation toxicity study showed only transient effects at a concentration of 5.35mg/litre."

"Groups of five male Sprague-Dawley rats received a single oral dose, by stomach tube, of 10.0, 31.6, 100, 316, 1000 or 3160 mg/kg bw of a suspension of Cellan 300 (refined alpha-cellulose) in either distilled water or Mazola corn oil. The animals were observed for 7 days following administration. No differences were observed among the groups as regards the average body weight, appearance and behaviour compared to untreated rats. No observable gross pathology was revealed at autopsy in animals dosed with either suspension. Therefore,the acute oral LD50 was >3160 mg/kg."

"Similar single doses of refined alpha-cellulose were given i.p. in distilled water suspension to five male rats. During 7 days observation there were no abnormalities in the rats given 316 mg/kg bw or less. At 1000 and 3160 mg/kg bw inactivity, laboured respiration and ataxia were observed 10 min after administration and, at 3160 mg/kg bw, ptosis and sprawling of the limbs were observed. These animals appeared normal after 24 hours and for the remainder of the observation period. At sacrifice body weights were higher than normal and gross autopsy revealed adhesions between the liver, diaphragm and peritoneal wall and congestion of the kidneys. Masses resembling unabsorbed compound were also observed and these were found to a small extent in the mesentery of the animals administered 316 mg/kg bw. There were no deaths and therefore the acute i.p. LD50 was >3160 mg/kg bw."

"Ten male and ten female Sprague-Dawley rats fasted overnight were fed Avicel RCN-15 (a mixture of 85% microcrystalline cellulose with 15% guar gum) at a dose level of 5000 mg/kg bw mixed with parmesan cheese. Six of ten males and five of ten females consumed the mixture within 24 hours. After a 14-day period during which all rats gained weight normally they were killed. There were no gross lesions at necropsy. Under the specified conditions of administration the LD50 was >5000 mg/kg bw."

As taken from WHO Food Additives Series 40 available at http://www.inchem.org/documents/jecfa/jecmono/v040je03.htm

5.2. Repeated dose toxicity

"Groups of four male rats were kept on diets containing 0.25, 2.5 or 25% of various edible celluloses for 3 months. No differences were observed among the groups with regard to growth and faecal output. Histopathology of the gastrointestinal tract revealed no treatment-related abnormalities."

"Three groups of five male rats received 0.5 or 10% microcrystalline cellulose in their diet for 8 weeks. Growth was comparable to controls but the 10% group showed slightly lower body weights. Haematology, serum chemistry and vitamin B1 levels in blood and faeces

showed no differences from controls."

"Groups of five male weanling Sprague-Dawley rats received 0, 5, 10 or 20% of acid-washed cellulose in their diet during three consecutive nutrient balance trials over a period of 17 days. Absorption of magnesium and zinc were significantly lower in the animals that were receiving the 10 and 20% cellulose diets. Histopathology of the gastrointestinal tract revealed increased mitotic activity and the presence of increased numbers of neutrophils in crypt epithelial cells, particularly of the duodenum and jejunum."

"A mixture of four types of Elceme (in the ratio of 1:1:1:1) was fed to groups of Wistar rats for 30 days at a dietary level of 50%, and for 90 days at a dietary level of 10% (Elceme is a microcrystalline cellulose, and the four types are identified by particle size, namely, 1-50 (powder), 1-100 (powder), 1-150 (fibrillar), 90-250 (granulate)). All test animals were observed for food intake and weight gain. For animals in the 10% group, urinalysis, haematological tests and serum biochemical tests were carried out at weeks 6 and 13 of the test. A complete autopsy including histopathology was carried out at the end of the study. Animals in the 50% group were subjected to a persorption test, on the last day of the study, by addition of a cellulose staining dye (Renal, Wine-red) to the food of the test animals at a level equivalent to 5% of the Elceme. The animals were sacrificed 24 hours after administration of the diet, and a careful histological examination was made of the gastrointestinal tract, spleen, liver, kidney and heart for stained particles. Animals in the 10% group gained significantly less weight than those in the control group; the marked decrease commenced in the third or fourth week of the study. Food intake was similar in test and control groups. Urinalysis, haematological values and biochemical values were similar for test and control group 1. At autopsy some of the rats on the test diet had distended stomachs, which often contained considerable amounts of the test diet. The absolute liver and kidney weights and the ratio of the weight of these organs to brain weight was increased in test animals when compared with control animals. No compound-related pathology was reported. Animals in the 50% group showed considerable less weight gain than control animals in spite of a marked increase in food consumption. No persorption of dyed fibres was observed."

"Randomly bred rats of both sexes were divided into groups that received a control diet or the control diet with 330 mg/kg microcrystalline cellulose for a period of 6 months. Six rats in each group were then killed, their organs were examined, and tissues were taken for histopathology. No effects of the treatment were observed."

"Groups of Crl:CD(R) BR/VAF/Plus rats (20/sex per group) were administered 0 (control), 25 000 or 50 000 mg/kg Avicel RCN-15 in the diet for 90 days. A few test animals were noted as having chromodacryorrhea/ chromorhinorrhea, but this was not considered to be biologically significant. In some early weeks the rats increased diet consumption, probably to allow for the increased dietary fibre content. Body weight gain was unaffected. During the study and at necropsy there was no evidence of treatment-related changes. Clinical chemistry, haematology and organ weights were unaffected by treatment. Histopathology of 34 organs or tissues, including gastrointestinal tract and gut-associated lymphoid tissue of the ileum, provided no evidence of toxicity of microcrystalline cellulose. The calculated daily consumption of microcrystalline cellulose was 3769 mg/kg bw per day for males and 4446 mg/kg bw per day for females. The author noted that the NOEL exceeded 50 000 mg/kgdiet

."

"Three groups of 50 male and 50 female rats received in their diet for 72 weeks either 30% ordinary cellulose or dry microcrystalline cellulose or micro-crystalline cellulose gel. Appearance and behaviour was comparable in all groups. No adverse effects were noted. The body weights of males given microcrystalline cellulose gel were higher than those of the controls. Food efficiency, survival and haematology were comparable in all groups. The liver and kidney weights of males receiving microcrystalline cellulose gel were higher than the controls. Gross and histopathology showed some dystrophic calcification of renal tubules in females on microcrystalline cellulose but all other organs appeared unremarkable. Tumour incidence did not differ between the groups."

"More studies have been done in which a group of rats was fed with a normal diet was compared to a second one fed with microcrystalline cellulose. The general conclusion is that cellulose addition to the normal diet has no effects on body weight (sometimes just a little weight gain for male rats in some studies), food consumption."

As taken from WHO Food Additives Series 40 available at http://www.inchem.org/documents/jecfa/jecmono/v040je03.htm

5.3. Reproduction toxicity

"Groups of eight male and 16 female rats were used to produce P, F1a, F1b, F2 and F3 generations after having been fed on diets containing 30% crystalline cellulose flour or gel or ordinary cellulose as a control. The presence in the diet of such an amount of non-nutritious material, which contributed no calories, had an adverse effect on reproduction. Fertility and numbers of live pups were relatively depressed, and lactation performances in all three generations, as well as survival and the physical condition of the pups, were unsatisfactory throughout the study. The new-born pups appeared smaller, weak and showed evidence of disturbed motor coordination. Liver weights were increased in the group receiving microcrystalline cellulose gel in all generations but other organ weights showed no consistent patterns. […]"

"Seventy-two rats (Sprague-Dawley CD) divided into eight groups were fed a mixture of four types of Elceme in the ratio of 1:1:1:1 in the diet at a level of 0, 2.5, 5 or 10% for 10 days, between days 6 and 15 of pregnancy. Rats of four test groups were killed on day 21 of pregnancy and the following parameters studied: number of fetuses and resorption sites, litter size and average weight of rats, average weight of fetuses and average backbone length. Fetuses were also examined for soft tissue or skeletal defects. The remaining groups were allowed to bear young, which were maintained to weaning (21 days). The following parameters were studied: litter size, weight of pups at days 7 and 21, and there was a histological study of the offspring. Although there is some suggestion that administration of dietary Elceme resulted in a dose-dependent increase in resorption sites, as well as a change in sex ratio, and possible defects such as opaque crystalline lenses,

the data has not been presented in a manner that permits a meaningful interpretation. However, the author concluded that Elceme is non-teratogenic."

"Groups of 25 presumed pregnant Crl:CD(R) BR VAF/Plus rats were administered 0 (control), 25 000 or 50 000 mg Avicel RCN-15/kg diet (equal to 2.1 and 4.5 g/kg bw per day, respectively) *ad libitum* on days 6 to 15 of gestation. Animals received basal diet at all other times. In the group receiving 50 000 mg/kg the food consumption on days 6 to 15 was significantly higher than that of controls, probably because of the increased fibre content. On day 20 of gestation the dams were killed by carbon dioxide inhalation and the following parameters studied: number and distribution of implantation sites, early and late resorptions, live and dead fetuses and corpora lutea. External, visceral and skeletal examinations of the fetuses were also performed. There was no evidence of any adverse effects of the test material on either the dams or the fetuses."

"[…] The parameters studied and examinations performed were the same as in the study of Freeman (1992b). There was no evidence of any effects of the Avicel treatment on the fetuses, and there was no evidence of a change of sex ratio in the pups or of eye defects. Under the conditions of the study, the maternal and fetal NOEL was > 50 000 mg/kg diet (equal to 4.6 g/kg bw per day)."

"At autopsy female rats of all generations showed kidney changes comprising pitting, occasional enlargement and zonation of the cortex. Other organs showed no consistent changes. No teratological deformities were seen."

As taken from WHO Food Additives Series 40 available at http://www.inchem.org/documents/jecfa/jecmono/v040je03.htm

"No adverse effects were found on reproduction or neonate development in rats and mice. Therefore, no adverse health effects in humans are expected from exposure to purified cellulose." As taken from Anderson RL et al. Cancer Lett., 1992, Apr 15, 63(2):83-92 available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=1562993&query_hl=30&itool=pubmed_docsum

5.4. Mutagenicity

"Various microcrystalline cellulose preparations have been tested for genotoxicity in several different assay systems. The results, all of which were negative" As taken from WHO Food Additives Series 40 available at http://www.inchem.org/documents/jecfa/jecmono/v040je03.htm

5.5. Cytotoxicity

“Cytotoxicity and CYP1A induction properties of celluloses and wood chips were studied with a teleost liver cell line, PLHC-1. Cells were exposed to acetone extracts of celluloses produced using new bleaching techniques (elemental chlorine free, ECF; totally chlorine free, TCF) in two sulphate mills or without any bleaching (unbleached, UB) in a sulphite mill. In another set of exposures, celluloses (ECF and TCF bleached) and wood chips (from pine and birch) were collected from a sulphate mill, extracted with acetone, and the extracts used to treat the cells. After exposure, O-deethylation of 7-ethoxyresorufin (EROD, a measure of cytochrome P4501A (CYP1A) catalytic activity), and total protein content, a measure of cytotoxicity, were assayed. The presence of the CYP1A protein in the exposed cells was assessed by immunoblotting. The cellulose and wood chip extracts were able to cause both cytotoxicity and EROD induction in the PLHC-1 cells. In the exposures conducted with the material from three different mills, the celluloses made of birch were more cytotoxic and more potent inducers of EROD activity than were the celluloses of pine. Further, UB celluloses increased EROD activity and caused cytotoxicity at lower doses than material bleached with modern bleaching techniques. In the exposures made with material from one single mill, there were no clear trends between the celluloses made of pine or birch. Wood chips of pine, however, were more cytotoxic than wood chips of birch. Especially with pine wood chips, cytotoxicity interfered with the induction of EROD activity, thus complicating the evaluation of CYP1A induction. CYP1A protein content was not detected in cells exposed to extracts of celluloses or wood chips, possibly due to low amounts of protein available for the assay. Wood and pulp processing, like bleaching, may change the chemical composition of the raw material in a way that reduces the potency for biological effects of the final product, cellulose. This could explain why both UB celluloses and wood chips were more potent in the cells than ECF or TCF bleached celluloses. In this study the PLHC-1 cell line showed its potential for use in evaluating the biological activity existing in pulp and paper mill products and raw materials. The identity and source of the compounds that were able to affect the PLHC-1 cell line remain to be determined” (Huuskonen et al., 1998).

5.6. Carcinogenicity

“The effect of artifical diets containing varied concentrations of either wheat bran or pure cellulose fibre on the induction of mammary tumours by *N*-nitrosomethylurea (i.v., 40 mg/kg) was studied in female F344 rats. The wheat bran diet appeared to possess anti-promotion properties that pure cellulose lacked. The concentrations of serum estrogens, urinary estrogens and faecal estrogens did not vary in a consistent, statistically significant manner.”

“The effect of a high-fibre diet containing 45 000 mg/kg Avicel PH-105 on the development of colon tumours was investigated in male Wistar rats that were injected with 1,2-dimethylhydrazine dihydrochloride (25 mg/kg, s.c., once weekly for 16 weeks). The test and

control diets were administered for 2 weeks prior to the first injection of the carcinogen. There was a reduction in the number of animals bearing colon tumours and a statistically significant reduction in the number of colon tumours/rat in the high-fibre dietary group. However, for small bowel tumours and tumours of the ear canal there was no significant difference between the dietary groups."

"Similarly, microcrystalline cellulose has been associated with the formation of granulomas in human lung when it has been injected intravenously during drug abuse. No such lesions have been described as a consequence of oral igestion of microcrystalline cellulose by rats or humans."

As taken from WHO Food Additives Series 40 available at http://www.inchem.org/documents/jecfa/jecmono/v040je03.htm

"Most of the available cohort and case-control studies of cancer of the nasal cavities and paranasal sinuses have shown increased risks associated with exposure to wood dust. Very high relative risks for adenocarcinoma at this site, associated with exposure to wood dust, have been observed in many countries."
Record for cellulose (CAS RN 9004-34-6):

Species:	RAT
Strain/Sex:	F344/FEMALE
Route:	SUBCUTANEOUS IMPLANT
Dose:	10 X 20 X 0.3 MM SHEETS IMPLANTED INTO 2 SITES IN LATERAL ABDOMINAL REGION AND 1 SITE ON THE BACK (STUDY DURATION: 741 D)
Results:	NEGATIVE
Reference:	[HATANAKA,S, ONEDA,S, OKAZAKI,K, SHONG,L, YOSHIDA,A, ISAKA,H AND YOSHIDA,H; INDUCTION OF MALIGNANT FIBROUS HISTIOCYTOMA IN FEMALE FISHER RATS BY IMPLANTATION OF CYANOACRYLATE, ZIRCONIA, POLYVINYL CHLORIDE OR SILICONE; IN VIVO 7(2):111-115, 1993]

Tumor Inhibition Studies:

Species:	RAT
Number of Animals Tested:	(30,28)/(20,19)

Strain/Sex:	SPRAGUE-DAWLEY/MALE
Dose (Inhibitor):	0; 1.5% IN DIET FOR 14 WK BEGINNING 3 D PRIOR TO CARCINOGEN TREATMENT (STUDY DURATION: 26 WK)
Route (Inhibitor):	ORAL
Carcinogen:	1,2-DIMETHYLHYDRAZINE ; 540-73-8
Route (Carcinogen):	SUBCUTANEOUS
Dose (Carcinogen):	20 MG/KG BW 1/WK FOR 12 WK
Promoter:	NONE USED
Target Tissue: Type of Lesion:	INTESTINE: CARCINOMA
Endpoint (Incidence):	23/28 (82%), 14/19 (74%), 10%, NOT SIGNIFICANT
Endpoint (Multiplicity):	1.1, 1.6, -45%, NOT SIGNIFICANT
Comments:	DIFFERENCES IN BODY WEIGHTS BETWEEN GROUPS WERE NOT SIGNIFICANT.
Reference:	[YAMAMOTO,I, MARUYAMA,H AND MORIGUCHI,M; EFFECT OF B-CAROTENE, SODIUM ASCORBATE AND CELLULOSE ON 1,2-DIMETHYLHYDRAZINE-INDUCED INTESTINAL CARCINOGENESIS IN RATS; CANCER LETT. 86(1):5-9, 1994]

As taken from CCRIS powered by Toxnet, available at https://toxnet.nlm.nih.gov/newtoxnet/ccris.htm

5.7. Irritation/immunotoxicity

No data available to us at this time.

5.8. All other relevant types of toxicity

“Intravenous abuse of drugs available in tablet form has led to the detection of excipients, e.g., talc, magnesium stearate or microcrystalline cellulose, in the tissues of a series of 33 fatality cases of intravenous drug addicts. Microcrystalline cellulose (21 cases) and talc (31 cases) were detected most frequently and, in some cases, were associated with granulomatous lesions.”

“A double-blind cross-over trial of the effects of guar gum and microcrystalline cellulose on metabolic control and serum lipids in 22 Type 2 diabetic patients has been carried out. The fibre preparations were given at 15 g/day for a 2-week period and then at 5 g/day for the remaining 10-week period of each treatment phase. There was no effect of the microcrystalline cellulose diet on fasting blood glucose level, glycosylated haemoglobin, serum HDL-cholesterol, serum triglycerides, serum zinc or ferritin, or urinary magnesium excretion.”

“The effect of various dietary fibres, including microcrystalline cellulose (40 g), on the uptake of vitamin A (approximately sixty times the daily requirement) from a test meal was investigated in 11 female subjects aged 19 to 22. All the dietary fibres significantly increased the absorption of the vitamin A over a period of 9 hours.”

“A study of apparent mineral balance in a group of eleven men revealed that there was no significant effect of cellulose, added to the diet at 7.5 g per 1000 kcal for 4 weeks, on the mineral balance of calcium, magnesium, manganese, iron, copper or zinc. However, in this report the source of the cellulose fibre was not specified.”

“The addition of nutritional grade cellulose (21 g) to the daily diet of healthy adolescent girls resulted in reduction of the serum calcium, phosphorus and iron concentrations. The authors suggested that high-fibre diets may not be advisable.”

As taken from WHO Food Additives Series 40 available at

http://www.inchem.org/documents/jecfa/jecmono/v040je03.htm

6. Functional effects on

6.1. Broncho/pulmonary system

“An acute inhalation toxicity study using a preparation of Avicel AC-815 (composed of 85% microcrystalline cellulose and 15% calcium alginate) with mass median aerodynamic

diameter of 8.48-8.61 µm (range of measures) was dispersed and delivered at a mean concentration of 5.35 mg/litre in a nose-only inhalation exposure chamber to 5 male and 5 female Crl:CDBR VAF Plus rats for a period of 4 hours. The rats were observed over the 14 days after removal from the chamber. The only signs of toxicity were on removal from the chamber and consisted of chromodacryorrhea, chromorhinorrhea and, in one male rat, decreased locomotion; these signs had resolved by the next day. After 14 days no gross lesions were observed at necropsy."

"[…] microcrystalline cellulose has been associated with the formation of granulomas in human lung when it has been injected intravenously during drug abuse. No such lesions have been described as a consequence of oral ingestion of microcrystalline cellulose by rats or humans […]."

"In one case intravenous abuse of the drug pentazocine, possibly for longer than six months, led to a fatal pulmonary granulomatosis."

As taken from WHO Food Additives Series 40 available at http://www.inchem.org/documents/jecfa/jecmono/v040je03.htm

"The lung-damaging effect of intratracheally administered cellulose was studied by biochemical and histological methods. Cell count, protein, phospholipid, lactate dehydrogenase and acid phosphatase were determined in bronchoalveolar lavage fluid 1, 3 and 7 days after intratracheal instillation. Histological tests were performed after days 1, 3 and 30. In vitro, cellulose did not damage the macrophage cells. In vivo, interstitial oedema as well as the initial signs of inflammation could be detected in the lung after the first day. Inflammation after 1 week could be noted, partly interstitial and partly intra-alveolar and intrabronchial. In the bronchoalveolar lavage fluid, protein, lactate dehydrogenase, acid phosphatase, phospholipid and cell count were enhanced after days 1 and 3. After 1 month, the developing bronchioalveolitis is fibrous in character. Contrary to the in vivo study, cellulose did not damage rat peritoneal macrophages." As taken from Adamis Z et al. J Appl Toxicol. 1997 Mar-Apr;17(2):137-41. PubMed available at http://www.ncbi.nlm.nih.gov/pubmed/9183058

6.2. Cardiovascular system

No data available at this time.

6.3. Nervous system

No data available at this time.

6.4. Other organ systems, dependent on the properties of the substance

“A number of clinical studies using refined cellulose as roughage in the human diet for the treatment of constipation showed no deleterious effects. Groups of 18 children received regular amounts of edible cellulose instead of normal cereal for three months. The only effect noted was an increase in bowel movements but no diarrhoea or other gastrointestinal disturbances were seen.”
As taken from WHO Food Additives Series 40 available at http://www.inchem.org/documents/jecfa/jecmono/v040je03.htm

“Eight male and eight female volunteers supplemented their normal diet with 30 g microcrystalline cellulose per day as either dry powder or gel (15% aqueous) for 6 weeks followed by 2 weeks without supplementation. No adverse findings were reported regarding acceptance or body weight but most subjects complained of fullness and mild constipation. Haematology was normal in all subjects. Biochemical blood values showed no differences between treatment and control periods, nor was there evidence of liver or kidney function disturbance. Urinalysis produced normal findings. The faecal flora remained unchanged. The cellulose content of faeces increases five to eight times during the test period. Microscopy revealed the presence of microcrystalline cellulose.”

As taken from WHO Food Additives Series 40 available at http://www.inchem.org/documents/jecfa/jecmono/v040je03.htm

7. Addiction

JTI is not aware of any information that demonstrates that this ingredient has any addictive effect.

8. Burnt ingredient toxicity

This ingredient was considered as part of an overall safety assessment of ingredients added to tobacco in the manufacture of cigarettes. An expert panel of toxicologists reviewed the open literature and internal toxicology data of 5 tobacco companies to evaluate a composite list of ingredients used in the manufacture of cigarettes. The conclusion of this report was that these ingredients did not increase the inherent biological activity of tobacco cigarettes, and are considered to be acceptable under conditions of intended use (Doull et al., 1994 & 1998).

Tobacco smoke condensates from cigarettes containing cellulose and an additive free, reference cigarettes were tested in a battery of *in vitro* and/or *in vivo* test(s). Within the sensitivity and specificity of the bioassay(s) the activity of the condensate was not changed by the addition of cellulose. Table below provides tested level(s) and specific endpoint(s).

Endpoint	Tested level (ppm)	Reference
Smoke chemistry	9,625	Baker et al., 2004a
In vitro genotoxicity	28,400	Baker et al., 2004c
In vitro cytotoxicity	28,400	Baker et al., 2004c
Inhalation study	28,400	Baker et al., 2004c

In comparison with a CSC of a reference cigarette with sideseam adhesives/cigarette paper corresponding to representative specifications for the majority of commercial cigarettes no differences were observed either in the bacterial mutagenicity, cytotoxicity or mammalian cell genotoxicity of the smoke condensate prepared from cigarettes with sideseam adhesives/cigarette paper containing Pulp, Cellulose at 27.2238 mg/cig. The smoke chemistry data between test and reference cigarette revealed small changes towards both higher and lower yields per cigarette over all analytical groups. These differences were well within the variability of the analytical methods (JTI NTM Study Report(s)).

Transfer studies:

“For cellulose in cigarette paper, transfer rates to TPM and gas phase were 9.7% and 20.4% respectively” (Jenkins et al 1980).

Cellulose applied to tobacco blend increased TPM yield and gas phase levels of furan, 2-methylfuran, dimethylfuran, furfuryl alcohol, furfural, 5-methylfurfural, acetaldehyde,

propionaldehyde, isobutyraldehyde, crotonaldehyde, acrolein, 2-butanone, 3-butene-2-one, pentadiene and methyl acetate (Wakeham & Silberman 1966).

A casing containing cellulose, glycerol and invert sugar, added to cigarettes made from tobacco sheet, reduced smoke yields of tar, water, nicotine, phenol, acetaldehyde, acrolein, isoprene, hydrogen cyanide, formaldehyde, carbon monoxide, carbon dioxide and catechol. Isoprene, nitrogen oxide, benzo(a)pyrene, indole and neophytadiene yields increased. Adding cellulose (10%) to cigarettes, did not affect the cytotoxicity or tumourigenicity of smoke condensate, or the ciliatoxicity of smoke (NCI Report No 4 1980).

Tobacco sheets containing cellulose and other ingredients, reduced cigarette smoke yields of tar, nicotine, carbon monoxide, phenol, polyaromatic hydrocarbons and carbonyl compounds (Prouse *et al* 1977; Briskin 1979; Eicher & Muller 1985). Benzo(a)pyrene yield increased (Dontenwill *et al* 1976).

Adding cellulose to reconstituted tobacco sheet did not increase cigarette smoke condensate bacterial mutagenicity (Burke 1979).

9. Heated/vapor emissions toxicity

No data available to us at this time.

10. Ecotoxicity

10.1. Environmental fate

The Ecological Categorization Results from the Canadian Domestic Substances List simply state that pulp, cellulose (CAS RN 65996-61-4) is of uncertain persistence in the environment.

Data accessed March 2017 on the OECD website:
http://webnet.oecd.org/CCRWeb/Search.aspx

10.2. Aquatic toxicity

The Ecological Categorization Results from the Canadian Domestic Substances List simply state that pulp, cellulose (CAS RN 65996-61-4) is not inherently toxic to aquatic organisms and is of low ecotoxicological concern.

Data accessed March 2017 on the OECD website: http://webnet.oecd.org/CCRWeb/Search.aspx

10.3. Sediment toxicity

No data available at this time.

10.4. Terrestrial toxicity

No data available at this time.

10.5. All other relevant types of ecotoxicity

The Ecological Categorization Results from the Canadian Domestic Substances List simply state that pulp, cellulose (CAS RN 65996-61-4) is of uncertain bioaccumulative potential in the environment.

Data accessed March 2017 on the OECD website: http://webnet.oecd.org/CCRWeb/Search.aspx

Pulp, cellulose is a “substance that is derived from natural products or materials, and which is not bioaccumulative or toxic. The natural decay and/or breakdown of this substance is unlikely to cause harm in the environment.”

As taken from NICNAS, 2017

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13. Last audited

April 2019

I U C L I D

D a t a s e t

Existing Chemical	Substance ID: 65996-61-4
CAS No.	65996-61-4
EINECS Name	Pulp, cellulose
EINECS No.	265-995-8
Molecular Formula	(C6H10O5)n

Dataset created by: EUROPEAN COMMISSION – European Chemicals Bureau

This dossier is a compilation based on data reported by the European Chemicals Industry following 'Council Regulation (EEC) No. 793/93 on the Evaluation and Control of the Risks of Existing Substances'. All (non-confidential) information from the single datasets, submitted in the IUCLID/HEDSET format by individual companies, was integrated to create this document.

The data have not undergone any evaluation by the European Commission.

Creation date: 19-FEB-2000

Number of Pages: **13**

Chapters: **all**

Edition: **Year 2000 CD-ROM edition**

Flags: **non-confidential**

1.0.1 OECD and Company Information

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Name: UCB Films La Cellophane Española, S.A.
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Street: Postfach 1515
Town: 29655 Walsrode
Country: Germany

Name: ZENECA Specialties
Street: PO Box 42
Town: M9 3DA Manchester
Country: United Kingdom

1.0.2 Location of Production Site

–

1.0.3 Identity of Recipients

–

1.1 General Substance Information

Substance type: natural substance
Physical status: solid

Substance type: organic
Physical status: solid

1.1.1 Spectra

–

1.2 Synonyms

Linters cellulose, poly–ß–1.4–D–glucosane, cotton linters pulp.
Source: BUCKEYE CELLULOSE GMBH Glückstadt

Pasta Dissolving, Pasta Alfa
Source: UCB Films La Cellophane Española, S.A. Burgos

Zellstoff, Papierzellstoff
Source: Hannover Papier Alfeld
Nordland Papier AG Dörpen
Stora Spezialpapiere GmbH Flensburg
SCHWÄBISCHE ZELLSTOFF AG Ehingen

1.3 Impurities

–

1.4 Additives

-

1.5 Quantity

Quantity more than 1 000 000 tonnes

1.6.1 Labelling

-

1.6.2 Classification

-

1.7 Use Pattern

Type: type
Category: Use in closed system

Type: type
Category: Use resulting in inclusion into or onto matrix

Type: industrial
Category: Basic industry: basic chemicals

Type: industrial
Category: Chemical industry: used in synthesis

Type: industrial
Category: Paper, pulp and board industry

Type: use
Category: Intermediates

Type: use
Category: other

1.7.1 Technology Production/Use

-

1.8 Occupational Exposure Limit Values

Type of limit: MAK (DE)
Limit value: 6 mg/m3
Remark: The MAK-value cited above refers to dust in general and not concretely to clp dust (see TRGS 900).
Source: BUCKEYE CELLULOSE GMBH Glückstadt

Type of limit: TLV (US)
Limit value: 10 mg/m3
Source: UCB Films La Cellophane Española, S.A. Burgos

Type of limit:
Limit value:
Source: Hannover Papier Alfeld

1.9 Source of Exposure

Source: UCB Films La Cellophane Española, S.A. Burgos

Remark: Aus Zellstoff wird überwiegend Papier hergestellt, welches überall und zu allen möglichen Zwecken, bis hin zur Lebensmittelverpackung, verwendet wird. Mensch und Umwelt sind also praktisch unbegrenzt exponiert.
Source: Hannover Papier Alfeld

Remark: Aus Zellstoff wird ueberwiegend Papier hergestellt, welches ueberall und zu allen moeglichen Zwecken, bis hin zur Lebensmittelverpackung, verwendet wird. Mensch und Umwelt sind also praktisch unbegrenzt exponiert.
Source: Stora Spezialpapiere GmbH Flensburg

Remark: Aus Zellstoff wird überwiegend Papier hergestellt, welches überall und zu allen möglichen Zwecken, bis hin zur Lebens-mittelverpackung, verwendet wird. Zellstoff ist in weiter-verarbeiteter Form als Verbrauchsgut sehr verbreitet.
Source: SCHWÄBISCHE ZELLSTOFF AG Ehingen

Remark: Source of exposure is every mechanical desintegration of thefibrous material regardless its form produced (bulk or sheet).
As a respiratory protective equipment in dusty areas it is recommended to wear a dust protection mask (filter P1).
Source: BUCKEYE CELLULOSE GMBH Glückstadt

1.10.1 Recommendations/Precautionary Measures

-

1.10.2 Emergency Measures

-

1.11 Packaging

-

1.12 Possib. of Rendering Subst. Harmless

-

1.13 Statements Concerning Waste

-

1.14.1 Water Pollution

-

1.14.2 Major Accident Hazards

-

1.14.3 Air Pollution

-

1.15 Additional Remarks

Remark: Zellstoff wird bei Hannover Papier integriert weiterverarbeitet zu Papier. Andere Hersteller trocknen den Zellstoff und versenden ihn mit ca. 90 % Trockenanteil (Rest Wasser). Hannover Papier kauft große Mengen solchen fremd hergestellten Zellstoffs über Händler und Importeure ein und erzeugt daraus Papier. Der Transport erfolgt mit allen möglichen Transportmitteln (Schiff, Bahn, Auto/LKW) als normales Frachtgut ohne jede Einschränkung. Neben der weit verbreiteten Wiederverwendung zur erneuten Papierherstellung kann Papier über alle denkbaren Wege gefahrlos entsorgt werden, z. B. Verbrennung, Deponierung, Kompostierung.
Source: Hannover Papier Alfeld

Remark: Es handelt sich bei dem importierten Zellstoff um Sulfatzellstoff, während es sich bei dem des vorgenannten Herstellers um Sulfitzellstoff handelt. Da es sich bei den genannten Stoffen nur um unterschiedliche Aufschlußmethoden handelt, sind die chemischen und physikalischen Eigenschaften des Produktes (Zellstoff) vergleichbar. Der vollständige Datensatz des genannten Herstellers kann deswegen auch für die Importe verwendet werden.
Source: Stora Reisholz GmbH Düsseldorf

Remark: siehe Meldung Hannoversche Papierfabriken
Source: Nordland Papier AG Dörpen

Remark: Der Zellstoff wird bei Stora Spezialpapiere GmbH zu Papier weiterverarbeitet. Der Transport erfolgt mit allen moeglichen Transportmitteln (Schiff, Bahn, LKW) als normales Frachtgut ohne jede Einschraenkung. Neben der weitverbreiteten Wiederverwendung zur erneuten Papierherstellung kann Papier ueber alle denkbaren Wege gefahrlos entsorgt werden, z.B. durch Verbrennung, Deponierung oder Kompostierung.
Source: Stora Spezialpapiere GmbH Flensburg

Remark: Der bei SCHWABEN ZELL erzeugte Zellstoff wird zu ca. 70 – 75 % integriert zu Papier weiterverarbeitet. 25 – 30 % der Zellstoffproduktion werden für den Markt getrocknet und mit einem Trockenanteil von 83 – 90 % (Rest Wasser) an Weiterverarbeiter geliefert. SCHWABEN ZELL kauft auch fremd hergestellten Zellstoff über Händler und Importeure ein und erzeugt daraus Papier. Der Transport erfolgt mit allen möglichen Transportmitteln (Schiff, Bahn, Auto/LKW) als normales Frachtgut ohne jede Einschränkung. Neben der weit verbreiteten Wiederverwendung zur erneuten Papierherstellung kann Papier über alle denkbaren Wege gefahrlos entsorgt werden, z.B. Verbrennung, Deponierung, Kompostierung.
Source: SCHWÄBISCHE ZELLSTOFF AG Ehingen

Source: SCHWÄBISCHE ZELLSTOFF AG Ehingen

Remark: Linters cellulose is a polymeric natural substance. Since natural polymers should not be listed in EINECS only chapter 1 of this HEDSET questionnaire will be completed.
Source: BUCKEYE CELLULOSE GMBH Glückstadt

1.16 Last Literature Search

–

1.17 Reviews

–

1.18 Listings e.g. Chemical Inventories

–

2.1 Melting Point
-

2.2 Boiling Point
-

2.3 Density
-

2.3.1 Granulometry
-

2.4 Vapour Pressure
-

2.5 Partition Coefficient
-

2.6.1 Water Solubility
-

2.6.2 Surface Tension
-

2.7 Flash Point
-

2.8 Auto Flammability
-

2.9 Flammability
-

2.10 Explosive Properties
-

2.11 Oxidizing Properties
-

2.12 Additional Remarks

Remark: Cellulose is a natural occuring polymer.
Polymers should not have been included in EINECS, therefore only chapter 1 of the Hedset dossier will be submitted.

Source: Wolff Walsrode AG Walsrode

3.1.1 Photodegradation

–

3.1.2 Stability in Water

–

3.1.3 Stability in Soil

–

3.2 Monitoring Data (Environment)

–

3.3.1 Transport between Environmental Compartments

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3.3.2 Distribution

–

3.4 Mode of Degradation in Actual Use

–

3.5 Biodegradation

–

3.6 BOD5, COD or BOD5/COD Ratio

–

3.7 Bioaccumulation

–

3.8 Additional Remarks

Remark: Cellulose is a natural occuring polymer.
Polymers should not have been included in EINECS, therefore only chapter 1 of the Hedset dossier will be submitted.
Source: Wolff Walsrode AG Walsrode

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

–

4.2 Acute Toxicity to Aquatic Invertebrates

–

4.3 Toxicity to Aquatic Plants e.g. Algae

–

4.4 Toxicity to Microorganisms e.g. Bacteria

–

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

–

4.5.2 Chronic Toxicity to Aquatic Invertebrates

–

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Soil Dwelling Organisms

–

4.6.2 Toxicity to Terrestrial Plants

–

4.6.3 Toxicity to other Non–Mamm. Terrestrial Species

–

4.7 Biological Effects Monitoring

–

4.8 Biotransformation and Kinetics

–

4.9 Additional Remarks

Remark: Cellulose is a natural occuring polymer.
Polymers should not have been included in EINECS, therefore only chapter 1 of the Hedset dossier will be submitted.
Source: Wolff Walsrode AG Walsrode

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity
-

5.1.2 Acute Inhalation Toxicity
-

5.1.3 Acute Dermal Toxicity
-

5.1.4 Acute Toxicity, other Routes
-

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation
-

5.2.2 Eye Irritation
-

5.3 Sensitization
-

5.4 Repeated Dose Toxicity
-

5.5 Genetic Toxicity 'in Vitro'
-

5.6 Genetic Toxicity 'in Vivo'
-

5.7 Carcinogenicity
-

5.8 Toxicity to Reproduction
-

5.9 Developmental Toxicity/Teratogenicity
-

5.10 Other Relevant Information

Type:
Remark: Cellulose is a natural occuring polymer.
Polymers should not have been included in EINECS, therefore only chapter 1 of the Hedset dossier will be submitted.
Source: Wolff Walsrode AG Walsrode

5.11 Experience with Human Exposure

-

7.1 Risk Assessment

-

SAFETY DATA SHEET

1. Identification

Product identifier **Bleached Southern Softwood Kraft Pulp – ARC, LRC**

Product list Leaf River 90/BSKP-ECF
Alabama River Softwood Pulp

Other means of identification

SDS number GP-S14

Recommended use The pulp is used in paper, tissue, filters and other specialty applications.

Recommended restrictions None known.

Manufacturer/Importer/Supplier/Distributor information

Company name GP Cellulose America Marketing LLC

Address 133 Peachtree Street, NE
Atlanta, GA 30303
United States

Telephone (M)SDS Request 404.652.5119

Website www.gpcellulose.com

E-mail MSDSREQ@GAPAC.COM

Emergency phone number Chemtrec - Emergency 800.424.9300

2. Hazard(s) identification

Emergency overview This product is not hazardous in the form in which it is shipped by the manufacturer but may become hazardous by downstream activities such as cutting, slitting, scarfing, hammer milling or otherwise working with this product that generate large amount of dusts. Those hazards are described below.

Physical hazards Not classified.

Health hazards Not classified.

Environmental hazards Not classified.

OSHA defined hazards Combustible dust

Label elements

Hazard symbol None.

Signal word Warning

Hazard statement The cutting, slitting, scarfing, hammer milling or otherwise working with this product may generate large amount of dusts that may form combustible dust concentrations in air.

Precautionary statement

Prevention Prevent dust accumulation and airborne dispersion of dust to minimize flash fire and explosion hazard. Keep away from heat, hot surfaces, sparks, open flames and other ignition sources. No smoking. Ground/bond container and receiving equipment. Follow good housekeeping practices; vacuum up areas where dust settles to avoid excessive accumulation of this combustible material. Use dust ignition proof vacuums for vacuuming combustible dusts. Observe good industrial hygiene practices.

Response Get medical advice/attention if you feel unwell. In case of fire: Use appropriate media to extinguish.

Storage Store away from strong oxidizers.

Disposal Dispose of waste and residues in accordance with local authority requirements.

Hazard(s) not otherwise classified (HNOC) None known.

Supplemental information None.

3. Composition/information on ingredients

Mixtures

Chemical name	Common name and synonyms	CAS number	%
CELLULOSE PULP		65996-61-4	84 - 94

Chemical name	Common name and synonyms	CAS number	%
WATER		7732-18-5	6 - 16

Since this material is converted into other products in varying operations, there may be a possibility of generating combustible dust under certain conditions. This SDS contains valuable information critical to the safe handling and proper use of the product. The SDS should be retained and available for employees and other users of this product.

4. First-aid measures

Inhalation If dust from the material is inhaled, remove the affected person immediately to fresh air. Call a physician if symptoms develop or persist. If persistent irritation, severe coughing or breathing difficulty occurs, seek medical attention.

Skin contact If irritation occurs, remove contaminated clothing and shoes; wash skin with soap and water. Wash clothing before reuse.

Eye contact Treat as a nuisance dust. Remove contact lenses and immediately rinse eyes with water for at least 15 minutes, occasionally lifting the upper and lower eyelids. If irritation persists, seek medical attention.

Ingestion Not likely, due to the form of the product. Get medical attention if symptoms occur.

Most important symptoms/effects, acute and delayed Direct contact with eyes and respiratory tract may cause temporary irritation.

Indication of immediate medical attention and special treatment needed Treat symptomatically.

General information Ensure that medical personnel are aware of the material(s) involved, and take precautions to protect themselves.

5. Fire-fighting measures

Suitable extinguishing media Type A Water Pressurized Extinguisher. Water fog. Foam. Dry chemical powder. Use a water spray to wet down paper dust to reduce the likelihood of ignition or dispersion of dust into the air. Extinguishers equipped with diffuser nozzles are desirable to minimize dust cloud generation.

Unsuitable extinguishing media None known.

Specific hazards arising from the chemical During fire, gases hazardous to health may be formed.

Special protective equipment and precautions for firefighters In the event of a fire, wear full protective clothing including a NIOSH-approved self-contained breathing apparatus (SCBA). Isolate the hazard area and deny entry to unnecessary and unprotected personnel. Self-contained breathing apparatus and full protective clothing must be worn in case of fire.

Fire fighting equipment/instructions Firefighters should wear full protective clothing including self-contained breathing apparatus.

Specific methods To avoid dust clouds, responders should use the extinguisher from as far away as possible and apply the extinguishing agent as gently as possible. The main considerations with hose stream operation are to avoid creating combustible dust clouds or introducing more air. In particular, the use of solid streams and direct dust pile hits can disperse dust into the air creating a potential flash fire hazard. The best way to apply water is in a medium to wide-pattern, as gently as possible. Responders should use a low nozzle pressure and loft the stream onto the burning material from as far away as the stream will reach.

General fire hazards In sufficient concentrations, fine dust dispersed in air at elevated temperatures or in the presence of an ignition source is a potential fire or dust explosion hazard. Airborne concentration of 15-200 g/m3 is often used as the minimum explosive concentration (MEC) or LFL.

6. Accidental release measures

Personal precautions, protective equipment and emergency procedures Use only non-sparking tools. Dust deposits should not be allowed to accumulate on surfaces, as these may form an explosive mixture if they are released into the atmosphere in sufficient concentration. Use a NIOSH/MSHA approved respirator if there is a risk of exposure to dust/fume at levels exceeding the exposure limits. Avoid inhalation of dust from the spilled material. Use personal protection recommended in Section 8.

Methods and materials for containment and cleaning up Eliminate all ignition sources. Isolate area. Wear appropriate personal protective equipment as specified in Section 8. If dust is generated, clean up material in a manner that does not disperse dust into the air. Use non-sparking tools and equipment. Reduce airborne dust and prevent scattering by wetting with water. Pick up spill for recovery or disposal and place in a closed container.

Environmental precautions No special environmental precautions required. Contact local authorities in case of spillage to drain/aquatic environment.

7. Handling and storage

Precautions for safe handling

Dry processing by mechanical means (such as cutting, slitting, scarfing, hammer milling) may generate combustible dust. Adequate controls should be implemented to prevent dust accumulation and ignition. Dust can form an explosive mixture with air in the presence of an ignition source. Dry powders can build static electricity charges when subjected to the friction of transfer and mixing operations. Provide adequate precautions, such as electrical grounding and bonding, or inert atmospheres. Maintain good housekeeping to keep formation of airborne dust to a minimum. Use with adequate ventilation. Use wet methods, if appropriate, to minimize dust generation and accumulation. Avoid contact with eyes, skin and clothing. Avoid inhalation or ingestion. Provide appropriate local exhaust ventilation at machinery and at places where dust can be generated.

Conditions for safe storage, including any incompatibilities

Keep away from heat, sparks and open flame. Prevent electrostatic charge build-up by using common bonding and grounding techniques. Store in original packaging in a cool, dry place out of direct sunlight. Keep in a well-ventilated place away from incompatible materials. Store away from strong oxidizers.

8. Exposure controls/personal protection

Occupational exposure limits

US. OSHA Table Z-1 Limits for Air Contaminants (29 CFR 1910.1000)

Components	Type	Value	Form
CELLULOSE PULP (CAS 65996-61-4)	PEL	5 mg/m3	Respirable fraction.
		15 mg/m3	Total dust.

US. ACGIH Threshold Limit Values

Components	Type	Value
CELLULOSE PULP (CAS 65996-61-4)	TWA	10 mg/m3

US. NIOSH: Pocket Guide to Chemical Hazards

Components	Type	Value	Form
CELLULOSE PULP (CAS 65996-61-4)	TWA	5 mg/m3	Respirable.
		10 mg/m3	Total

Biological limit values

No biological exposure limits noted for the ingredient(s).

Appropriate engineering controls

When using product, provide local and general exhaust ventilation to keep airborne dust concentrations below exposure limits. Provide explosion protection for air material separators (e.g. baghouses) collecting combustible dusts. Use wet methods, if appropriate, to reduce the generation of dust. Due to the explosive potential of paper dust when suspended in air, precautions should be taken to prevent sparks or other ignition source in ventilation equipment. Follow good housekeeping practices; vacuum up areas where dust settles to avoid excessive accumulation of this combustible material. Use dust ignition proof vacuums for vacuuming combustible dusts.

Individual protection measures, such as personal protective equipment

Eye/face protection

Goggles or safety glasses are recommended if the product is used in such a way as to generate high dust levels. Ensure compliance with OSHA's PPE standard (29 CFR 1910.132 and 133) for eye and face protection.

Skin protection

Hand protection

For prolonged or repeated skin contact use suitable protective gloves.

Other

Gloves and outer garments are recommended to minimize potential irritation from handling product. Launder clothing before reuse. Ensure compliance with OSHA's PPE standards (29 CFR 1910.132 (general) and 138 (hand protection).

Respiratory protection

Use a NIOSH/MSHA approved respirator if there is a risk of exposure to dust/fume at levels exceeding the exposure limits. Respirators should be selected by and used under the direction of a trained health and safety professional following requirements found in OSHA's respirator standard (29 CFR 1910.134) and ANSI's standard for respiratory protection (Z88.2).

Thermal hazards

Wear appropriate thermal protective clothing, when necessary.

General hygiene considerations

Always observe good personal hygiene measures, such as washing after handling the material and before eating, drinking, and/or smoking. Routinely wash work clothing and protective equipment to remove dust.

9. Physical and chemical properties

Appearance	Pulp.
Physical state	Solid.
Form	sheets
Color	White or Natural
Odor	Paper-like
Odor threshold	Not available.
pH	Not available.
Melting point/freezing point	Not applicable.
Initial boiling point and boiling range	Not applicable.
Flash point	Not applicable.
Evaporation rate	Not applicable.
Flammability (solid, gas)	Not available.
Upper/lower flammability or explosive limits	
Flammability limit - lower (%)	Not available.
Flammability limit - upper (%)	Not available.
Explosive limit - lower (%)	Not available.
Explosive limit - upper (%)	Not available.
Vapor pressure	Not applicable.
Vapor density	Not applicable.
Relative density	Not applicable.
Solubility(ies)	
Solubility (water)	Insoluble
Partition coefficient (n-octanol/water)	Not applicable.
Auto-ignition temperature	399.2 - 500 °F (204 - 260 °C)
Decomposition temperature	Not applicable.
Viscosity	Not applicable.
Other information	
Dust explosion properties	
St class	1
Molecular weight	(162)X
Specific gravity	1.27 - 1.61

10. Stability and reactivity

Reactivity	The product is stable and non-reactive under normal conditions of use, storage and transport.
Chemical stability	Product is stable under normal conditions of use.
Possibility of hazardous reactions	Not expected under normal conditions of use.
Conditions to avoid	Dust accumulation, dispersion of dust in air, high temperatures, open flame, sparks, or other sources of ignition.
Incompatible materials	Strong oxidizing agents.
Hazardous decomposition products	In a fire situation, carbon dioxide and carbon monoxide.

11. Toxicological information

Information on likely routes of exposure

Inhalation	Inhalation of dusts may cause respiratory irritation.
Skin contact	Frequent or prolonged contact may defat and dry the skin, leading to discomfort and dermatitis.

Eye contact	Dust generated during processing may cause eye irritation.
Ingestion	Ingestion is not likely to be a primary route of occupational exposure.
Symptoms related to the physical, chemical and toxicological characteristics	In its purchased form, the product is not hazardous. Dust generated during processing may cause eye and respiratory irritation. Coughing and difficulty breathing. Exposed individuals may experience eye tearing, redness, and discomfort.

Information on toxicological effects

Acute toxicity Data for ingredients found below.

Components	Species	Test Results
CELLULOSE PULP (CAS 65996-61-4)		
Acute		
Oral		
LD50	Rat	> 5000 mg/kg, days

Skin corrosion/irritation	Non-irritating in rabbits.
Serious eye damage/eye irritation	Minimally irritating in rabbits. Dust from processing may cause irritation.

Respiratory or skin sensitization

Respiratory sensitization	Not likely due to form of the product.
Skin sensitization	No evidence of skin sensitization in guinea pigs.
Germ cell mutagenicity	No evidence of mutagenicity or genotoxicity in vitro cell systems or rats.
Carcinogenicity	No evidence of carcinogenicity in rats or humans. None of this product's components are listed by ACGIH, IARC, OSHA, or NTP.

IARC Monographs. Overall Evaluation of Carcinogenicity

Not listed.

OSHA Specifically Regulated Substances (29 CFR 1910.1001-1052)

Not regulated.

US. National Toxicology Program (NTP) Report on Carcinogens

Not listed.

Reproductive toxicity	No evidence of reproductive or developmental effects in rats or humans.
Specific target organ toxicity - single exposure	No evidence of specific target organ effects in rats and humans. Dust generated during processing may cause respiratory irritation.
Specific target organ toxicity - repeated exposure	No evidence of specific target organ effects in rats and humans.
Aspiration hazard	Not likely to cause aspiration.
Chronic effects	Prolonged or repeated inhalation of dust or particles may impair lung function cause lung damage.
Further information	This product has no known adverse effect on human health. Data for similar material used to support Cellulose Pulp.

12. Ecological information

Ecotoxicity	The product is not classified as environmentally hazardous. However, this does not exclude the possibility that large or frequent spills can have a harmful or damaging effect on the environment.
Persistence and degradability	No data is available on the degradability of this product.
Bioaccumulative potential	Not available.
Mobility in soil	Not available.
Other adverse effects	No other adverse environmental effects (e.g. ozone depletion, photochemical ozone creation potential, endocrine disruption, global warming potential) are expected from this product.

13. Disposal considerations

Disposal instructions	Collect and reclaim or dispose in a manner that does not generate dust borne particles at licensed waste disposal site. Dispose of in a landfill or incinerate in accordance with federal, state, local and provincial regulations.
Local disposal regulations	Dispose in accordance with all applicable regulations.
Hazardous waste code	Not applicable. The product is not an EPA hazardous waste.

Waste from residues / unused products	Dispose of in accordance with local regulations. Empty containers or liners may retain some product residues. This material and its container must be disposed of in a safe manner (see: Disposal instructions).
Contaminated packaging	Not applicable.

14. Transport information

DOT

Not regulated as dangerous goods.

IATA

Not regulated as dangerous goods.

IMDG

Not regulated as dangerous goods.

Transport in bulk according to Annex II of MARPOL 73/78 and the IBC Code	Not available.
General information	This product is not regulated as a hazardous material by the United States (DOT) transportation regulations.

15. Regulatory information

US federal regulations	Paper (cellulose) dust, a combustible dust hazard generated from the handling and processing of paper, tissue and pulp, is considered hazardous and is regulated under the Hazard Communication Standard 29 CFR 1910.1200.

TSCA Section 12(b) Export Notification (40 CFR 707, Subpt. D)

Not regulated.

CERCLA Hazardous Substance List (40 CFR 302.4)

Not listed.

SARA 304 Emergency release notification

Not regulated.

OSHA Specifically Regulated Substances (29 CFR 1910.1001-1052)

Not regulated.

Superfund Amendments and Reauthorization Act of 1986 (SARA)

SARA 302 Extremely hazardous substance

Not listed.

SARA 311/312 Hazardous chemical	Yes
Classified hazard categories	Combustible dust

SARA 313 (TRI reporting)

Not regulated.

Other federal regulations

Clean Air Act (CAA) Section 112 Hazardous Air Pollutants (HAPs) List

Not regulated.

Clean Air Act (CAA) Section 112(r) Accidental Release Prevention (40 CFR 68.130)

Not regulated.

Safe Drinking Water Act (SDWA)	Not regulated.
US state regulations	California Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65): This material is not known to contain any chemicals currently listed as carcinogens or reproductive toxins.

International Inventories

Country(s) or region	Inventory name	On inventory (yes/no)*
Australia	Australian Inventory of Chemical Substances (AICS)	Yes
Canada	Domestic Substances List (DSL)	Yes
Canada	Non-Domestic Substances List (NDSL)	No
China	Inventory of Existing Chemical Substances in China (IECSC)	Yes
Europe	European Inventory of Existing Commercial Chemical Substances (EINECS)	Yes

Country(s) or region	Inventory name	On inventory (yes/no)*
Europe	European List of Notified Chemical Substances (ELINCS)	No
Japan	Inventory of Existing and New Chemical Substances (ENCS)	Yes
Korea	Existing Chemicals List (ECL)	Yes
New Zealand	New Zealand Inventory	Yes
Philippines	Philippine Inventory of Chemicals and Chemical Substances (PICCS)	Yes
Taiwan	Taiwan Toxic Chemical Substances (TCS)	Yes
United States & Puerto Rico	Toxic Substances Control Act (TSCA) Inventory	Yes

*A "Yes" indicates that all components of this product comply with the inventory requirements administered by the governing country(s)
A "No" indicates that one or more components of the product are not listed or exempt from listing on the inventory administered by the governing country(s).

16. Other information, including date of preparation or last revision

Issue date May-07-2015

Revision date May-30-2018

Version # 03

HMIS® ratings
Health: 0
Flammability: 1
Physical hazard: 0

NFPA ratings
Health: 0
Flammability: 1
Instability: 0

Disclaimer
This SDS is intended to quickly provide useful information to the user(s) of this material or product. It is not intended to serve as a comprehensive discussion of all possible risks or hazards, and it assumes a reasonable use of the product. The information contained in this SDS is believed to be accurate as of the date of preparation of this SDS and has been compiled from sources believed to be reliable. It is offered for your consideration, investigation and verification. The user or handler (or their employer) should consider the specific conditions in which this material will be used, handled, or stored and determine what specific safety or other precautions are required. Employers should ensure that their employees, agents, contractors, and customers who will use the product receive adequate warnings and safe handling procedures, including a current SDS. Product users or handlers (or their employer) who are unsure of what specific precautions are required should consult their employer, product supplier, or safety or health professionals before handling or working with this product. Please notify us immediately if you believe this SDS or other safety and health information about this product is inaccurate or incomplete.

Revision information
Product and Company Identification: Product and Company Identification
Hazard(s) identification: Prevention
Hazard(s) identification: Response
First-aid measures: Eye contact
First-aid measures: Ingestion
Fire-fighting measures: Specific methods
Accidental release measures: Personal precautions, protective equipment and emergency procedures
Handling and storage: Precautions for safe handling
Exposure controls/personal protection: Appropriate engineering controls
Toxicological information: Skin contact
Ecological information: Ecotoxicity
Disposal considerations: Hazardous waste code
GHS: Classification