CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

Substance Name: 475-glass special purpose fibres

EC Number: **Not assigned**

CAS Number: **Not assigned**

Index Number: **Not assigned**

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Part A.

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	475-glass special purpose fibres
EC number:	[1]
CAS number:	[1]
Annex VI Index number:	[1]
Degree of purity:	100%
Impurities:	N/A for UVCB substance

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation	**Directive 67/548/EEC (Dangerous Substances Directive; DSD)**
Current entry in Annex VI, CLP Regulation	Carc 2 – H351 with notes A, Q, R*	Carc. Cat. 3; R40 with notes A, Q, R
Current proposal for consideration by RAC	Carc. 2 – H351 (with note R)	Carc. Cat. 3; R40 (with note R)
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Carc. 2 – H351 (with note R)	Carc. Cat. 3; R40 (with note R)

* The text of the notes is given in section 2.1 of the CLH report.

[1] These identification numbers (EC number, CAS number and index number) are not specific of special-purpose glass fibre but correspond to a wide range of fibres. EC number: 266-046-0; CAS number: 65997-17-3 ; Index number: 650-016-00-2

1.3 Proposed harmonised classification and labelling based on CLP Regulation and/or DSD criteria

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	None		None	Not evaluated
2.2.	Flammable gases	None		None	Not evaluated
2.3.	Flammable aerosols	None		None	Not evaluated
2.4.	Oxidising gases	None		None	Not evaluated
2.5.	Gases under pressure	None		None	Not evaluated
2.6.	Flammable liquids	None		None	Not evaluated
2.7.	Flammable solids	None		None	Not evaluated
2.8.	Self-reactive substances and mixtures	None		None	Not evaluated
2.9.	Pyrophoric liquids	None		None	Not evaluated
2.10.	Pyrophoric solids	None		None	Not evaluated
2.11.	Self-heating substances and mixtures	None		None	Not evaluated
2.12.	Substances and mixtures which in contact with water emit flammable gases	None		None	Not evaluated
2.13.	Oxidising liquids	None		None	Not evaluated
2.14.	Oxidising solids	None		None	Not evaluated
2.15.	Organic peroxides	None		None	Not evaluated
2.16.	Substance and mixtures corrosive to metals	None		None	Not evaluated
3.1.	Acute toxicity - oral	None		None	Not evaluated
	Acute toxicity - dermal	None		None	Not evaluated
	Acute toxicity - inhalation	None		None	Not evaluated
3.2.	Skin corrosion / irritation	None		None	Not evaluated
3.3.	Serious eye damage / eye irritation	None		None	Not evaluated
3.4.	Respiratory sensitisation	None		None	Not evaluated
3.4.	Skin sensitisation	None		None	Not evaluated
3.5.	Germ cell mutagenicity	None		None	Not evaluated
3.6.	Carcinogenicity	Carc. 2 – H351		Carc. 2 – H351	
3.7.	Reproductive toxicity	None		None	Not evaluated
3.8.	Specific target organ toxicity –single exposure	None		None	Not evaluated
3.9.	Specific target organ toxicity	None		None	Not evaluated

	– repeated exposure				
3.10.	Aspiration hazard	None		None	Not evaluated
4.1.	Hazardous to the aquatic environment	None		None	Not evaluated
5.1.	Hazardous to the ozone layer	None		None	Not evaluated

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Signal word: "Warning"
Hazard statements: H351
Precautionary statements: not harmonised
Pictogram: SGH08

Proposed notes assigned to an entry: Note R. The text of the note is detailed in section 2.1 of the CLH report.

Table 4: Proposed classification according to DSD

Hazardous property	**Proposed classification**	**Proposed SCLs**	**Current classification [1)]**	**Reason for no classification [2)]**
Explosiveness	None		None	Not evaluated
Oxidising properties	None		None	Not evaluated
Flammability	None		None	Not evaluated
Other physico-chemical properties *[Add rows when relevant]*	None		None	Not evaluated
Thermal stability	None		None	Not evaluated
Acute toxicity	None		None	Not evaluated
Acute toxicity – irreversible damage after single exposure	None		None	Not evaluated
Repeated dose toxicity	None		None	Not evaluated
Irritation / Corrosion	None		None	Not evaluated
Sensitisation	None		None	Not evaluated
Carcinogenicity	Carc. Cat. 3; R40		Carc. Cat. 3; R40	
Mutagenicity – Genetic toxicity	None		None	Not evaluated
Toxicity to reproduction – fertility	None		None	Not evaluated
Toxicity to reproduction – development	None		None	Not evaluated
Toxicity to reproduction – breastfed babies. Effects on or via lactation	None		None	Not evaluated
Environment	None		None	Not evaluated

[1)] Including SCLs
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Indication of danger: Xn
R-phrases: R40
S-phrases: S45-53

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

In annex I, man-made vitreous fibres (MMVF) are currently subdivided in two different entries (see table below). **Special-purpose fibres** are explicitly mentioned in the phrasing of the MMVF entry that is classified Carc. 1B. However, the criteria used to discriminate between the two MMVF entries is the alkaline oxide and alkaline earth oxide content (K_{NB} index) and both E- and 475-glass fibres have a K_{NB} index **greater than 18%.** This was confirmed by industry at the TC C&L of October 2006 (doc ECBI/13/07 Rev. 2) that the composition of 475-glass fibres in K_{NB} is greater than 18% and close to the limit.

Index number	Substance Name	Classification	Nota
650-016-00-2	Mineral wool, with the exception of those specified elsewhere in this Annex; [Man-made vitreous (silicate) fibres with random orientation with alkaline oxide and alkali earth oxide ($Na_2O+K_2O+CaO+MgO+BaO$) content **greater than 18 %** by weight]	Carc. 2 – H351	A, Q, R
650-017-00-8	Refractory Ceramic Fibres; **Special Purpose Fibres**, with the exception of those specified elsewhere in this Annex; [Man-made vitreous (silicate) fibres with random orientation with alkaline oxide and alkali earth oxide ($Na_2O+K_2O+CaO+MgO+BaO$) content less or equal to 18 % by weight]	Carc. 1B – H350i	A, R

Based on the alkaline oxide and alkaline earth oxide content of 475-glass fibres, the current index number 650-016-00-2 would currently apply.

In this proposal for harmonised classification, 475-glass special purpose fibres are proposed to be classified as Carc. 2– H351 and to be assigned with the note R but not the notes A and Q.

In November 2005, a French proposal was submitted at the TC C&L for a classification of special purpose fibres E and 475 as Carc. Cat.2; R45. In October 2006, the TC C&L agreed to classify 'Type 475 Special purpose fibres' with Carc. Cat. 3; R40 and 'E-glass fibres' with Carc. Cat. 2; R49 classification. Discussions are added in annex of this dossier.

This decision was however not included in an ATP before the entry into force of CLP.

Since 2006, there were no new relevant studies of toxicology published on special purpose fibres 475.

There is no registration dossier on 475-glass fibres.

Justification for the proposal of a new specific entry:

For the reasons described above, we propose to have the following entries (according to the Follow-up III of TC C&L October 2006; doc ECBI/09/07):

- To keep the current entries Index 650-017-00-8 and Index 650-016-00-2 as they are.

- To create one additional entry for 475-fibres (with a new index number).

In the absence of specific CAS or EC number, the new entry needs to define in its phrasing what is a 475-glass special purpose fibre. 475-glass is mainly characterised by its chemical composition and consequently this information needs to be specified in the entry. However, the chemical composition alone may not be sufficient to characterise fully the 475-glass fibres.

To our knowledge, 475-glass may also be used in other type of glass fibres than special purpose fibres, such as for example continuous glass filaments, which have larger diameters (6 to 16 µm, CIRC 2002). Therefore, an appropriate way to identify the entries could be to specify both composition and size and to limit the entries to respirable fibres with a diameter inferior to 6 µm as specified in the note R. The following naming of the new specific entry, arising from the registration dossier and the Follow-up III of TC C&L October 2006 (doc ECBI/09/07) is proposed:

"Special purpose 475-glass fibres [Calcium-aluminium-silicate fibres with random orientation with the following composition (% given by weight): SiO_2 55.0-60.0%, Al_2O_3 4.0-7.0%, B_2O_3 8.0-11.0%, Na_2O 9.5-13.5%, K_2O 1.0-4.0%, CaO 1.0-5.0%, MgO 0.0-2.0%, Fe_2O_3 <0.2%, ZnO 2.0-5.0%, BaO 3.0-6.0%, F_2 <1.0% with note R." Process: Drawing or spinning the molten mix (at approx. 1500°C) from nozzles].

Proposal of notes:

The notes A and Q are not proposed for the specific entry of 475-glass special purpose fibres.

Note A applies in order to give the exact name of the substance on the label and not the name of the entry in the cases of generic entries. The new entry proposed is not a generic entry and note A is therefore not relevant.

Note Q applies for the general entry for fibres (index 650-016-00-2) to be able to distinguish fibres that are of less concern and should be exempted from the carcinogenic classification. However, the proposed new entry is based on data specific of 475-glass special fibres. The available data as shown in this dossier demonstrate the carcinogenic potential of these fibres and it is not relevant to include exemption conditions.

The note R is proposed for this new specific entry, as it was discussed and agreed at the TC C&L (ECBI/33/07, revision 1).

The note R applies for the fibres with a length weighted geometric mean diameter inferior to 6 µm. This diameter corresponds to respirable particles (the mass fraction of particles that reaches the alveoli), and is the most adapted way to limit the diameter of the 475-glass fibres for the new specific entry.

Text of notes:

A: Without prejudice to Article 17(2), the name of the substance must appear on the label in the form of one of the designations given in Part 3. In Part 3, use is sometimes made of a general description such as "... compounds" or "... salts". In this case, the supplier is required to state on the label the correct name, due account being taken of section 1.1.1.4.

Q : The classification as a carcinogen need not to apply if it can be shown that the substance fulfils one of the following conditions:

- a short term biopersistence test by inhalation has shown that the fibres longer than 20 μm have a weighted half-life less than 10 days; or
- a short term biopersistence test by intratracheal instillation has shown that the fibres longer than 20 μm have a weighted half-life less than 40 days; or
- an appropriate intra-peritoneal test has shown no evidence of excess carcinogenicity; or
- absence of relevant pathogenicity or neoplastic changes in a suitable long term inhalation test.

R : carcinogenic classification need not to apply to fibres with a length weighted geometric mean diameter – 2 standard geometric errors > 6 μm.

2.2 Short summary of the scientific justification for the CLH proposal

Experimental data for 475-glass fibres clearly provide evidence of a carcinogenic effect in several species (rats, hamsters and monkeys) and in both sexes in numerous independent studies in different laboratories. Tumours consist in both benign and malignant lung tumours (carcinomas, mesotheliomas and sarcomas) and abdominal tumours by different routes of exposure (inhalation, intraperitoneal, intratracheal and intrapleural).

Indeed, special-purpose fibres show a carcinogenic potential by the intraperitoneal, intratracheal and intrapleural routes. Fibre biopersistency may enable their migration further inhalation into the pleural cavity and emphasise the relevance of positive results by the intrapleural route.

No study clearly demonstrates the induction of tumour following inhalation of 475-glass fibres and most of the available studies show important limitations.

On the basis of animal studies by inhalation, E-glass fibres induce marked macrophage reaction, alveolar fibrosis and hyperplasia which may indicate a progressive pathway to neoplastic transformation of respiratory cells whereas 475-glass fibres do not exhibit such effects by inhalation (Cullen, 2000). Besides, comparison between the carcinogenic potential of both fibres by intraperitoneal route (Pott 1984) shows that 32% of rats has abdominal tumours with E-glass although only 4% of rats has abdominal tumours with 475-glass tumours.

2.3 Current harmonised classification and labelling

According to their chemical composition, 475-glass fibres are classified under index number 650-016-00-2 (see related classification in the table above).

2.4 Current self-classification and labelling

There is no registration dossier specifically on 475-glass fibres.

Moreover, the inventory of classification encompasses the large family of glass, oxides and chemicals but does not specify to which fibres they refer. It was therefore not possible to check for potential self-classification of 475-glass special purpose fibres.

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

475-glass fibres have CMR properties, i.e. carcinogenic property, that justifies a harmonised classification and labelling according to article 36 of CLP.

Considering the recommendations of TC C&L, harmonisation of classification on this handover CLH dossier is considered to be required for this endpoint (carcinogenicity) previously concluded by the TC C&L.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

475-glass is a member of the family calcium-aluminium-silicate glasses. Boron oxide is generally a major additive of 475-glass. 475-glass special purpose fibres are 475-glass fibres with special properties e.g. high corrosion resistance, high strength, low dielectric constant. In order to provide such special properties the composition is manipulated by adding or reducing specific oxide content.

Nota on fibre nomenclature (INSERM 1999)

The name 475 refers to the type of glass i.e. to a specific chemical composition (see 1.2 above).

These fibres are usually described as special purpose 475-glass fibre.

Special-purpose fibres are often named by a JM code. The code is in relation with the mean diameter of fibres and is not specific to a type of glass. The table below presents the possible type of glass by fibre code.

JM code	90	100	102	104	106	206	108 A	108 B	110	BX	210	112	212	CX
Fibre diameter (µm)	0.26	0.32	0.40	0.50	0.65	0.75	1.00	1.80	2.70	2.90	3.00	4.00	4.10	5.50
Type of glass	475	475	475 753	475 E 753	475 E 753	475 753	475 753	475 E 753	475 753	475 753	475 753	475	475	475 753

Size: diameter range: 0.26 to 5.50 µm (INSERM, 1999)

Fibre composition for special purpose 475-glass fibres according to the ECBI/10/05 Add.6:

Oxide component	475-glass fibres (diameter < 3 µm) (weight %)
SiO_2	55.0-60.0
Al_2O_3	4.0-7.0
B_2O_3	8.0-11.0
Na_2O	9.5-13.5
K_2O	1.0-4.0
CaO	1.0-5.0
MgO	0.0-2.0
Fe_2O_3	< 0.2
ZnO	2.0-5.0
BaO	3.0-6.0
F_2	< 1.0

*K_{NB}= MgO+CaO+ Na_2O+K_2O+BaO

The industry has confirmed at the TC C&L of October 2006 (doc ECBI/13/07 Rev. 2) that the composition of E-glass fibres in K_{NB} is greater 18% and close to the limit.

Table 5: Substance identity

EC number:	[2]
EC name:	[2]
CAS number (EC inventory):	-
CAS number:	[2]
CAS name:	-
IUPAC name:	IUPAC name not allocated
CLP Annex VI Index number:	[2]
Molecular formula:	Not applicable (a generic molecular formula cannot be provided for 475-glass fibres as it is a UVCB substance)
Molecular weight range:	Not applicable

Structural formula: Not applicable

1.2 Composition of the substance

Table 6: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
475-glass special purpose fibres	Ca 100%	-	-

Current Annex VI entry: index number 650-016-00-2

Table 7: Impurities (non-confidential information)

[2] These identification numbers (EC number 266-046-0, EC name: Glass, oxide, chemicals, CAS number 65997-17-3 and index number 650-016-00-2) are not specific in special-purpose glass fibre but correspond to a wide range of fibres.

Impurity	Typical concentration	Concentration range	Remarks
None	-	-	-

Table 8: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
None	-	-	-	-

1.2.1 Composition of test material

Not relevant.

1.3 Physico-chemical properties

Table 9: Summary of physico - chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
State of the substance at 20°C and 101,3 kPa	Inorganic, solid, white odourless fibrous glass in bulk or blanket form	ATSDR, 2004	measured
Melting/freezing point	> 650°C	ATSDR, 2004	estimated
Boiling point	Not applicable		
Relative density	2.6 g/cm³ at 20°C	AFSSET, 2007	measured
Softening point	850 °C	AFSSET, 2007	measured
Maximal temperature of use	600 °C	AFSSET, 2007	measured
Devitrification temperature	800 °C	AFSSET, 2007	measured
Not fibrous particles or shot	minimal	AFSSET, 2007	measured
Refractive index	1.55	AFSSET, 2007	measured
Vapour pressure	Not applicable		
Surface tension	Not applicable		
Water solubility	Not soluble in water	ATSDR, 2004	measured
Partition coefficient n-octanol/water	Not applicable		
Flash point	Not applicable		
Flammability	Not applicable		
Explosive properties	Not applicable		
Self-ignition temperature	Not applicable		
Oxidising properties	Not applicable		

Granulometry	aerodynamic diameters corresponding to the fibre density, diameter and length < 4 um	Cullen, 2000	measured
Stability in organic solvents and identity of relevant degradation products	Not applicable		
Dissociation constant	Not applicable		
Viscosity	Not applicable		

2 MANUFACTURE AND USES

2.1 Manufacture

Two European production sites are located for the one in Belgium (Hollingsworth & Vose) and the other one in Germany (Lauscha). (AFSSET, 2007)

2.2 Identified uses

Industrial: air and liquid filtration (ASHRAE, HEPA, ULPA filter) in automotive applications and electronic industry (clean room filter), separation (battery) and insulation in aeronautical applications.

General public: In the filtration of high-efficiency air, the major application is the general ventilation of buildings (offices, schools, airports, hotels, department stores, residences, conference center). Otherwise, the domestic applications of special purpose fibres are filters for vacuum cleaners and the purifiers of air.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Not evaluated in this dossier.

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

No data.

4.2 Acute toxicity

No data.

4.3 Irritation

4.3.1 Skin irritation

Discussions took place on this endpoint at the TC C&L, leading to the conclusion that the classification for the skin irritation has been removed.

No classification proposed.

4.4 Corrosivity

No data.

4.5 Sensitisation

No data.

4.6 Repeated dose toxicity (including biopersistency):

This endpoint is presented only for information and is not proposed for harmonized classification.

4.6.1 Non-human information

4.6.1.1 Repeated dose toxicity: oral

No data.

4.6.1.2 Repeated dose toxicity: inhalation

Species	Fibre type	Conc.			Expo. time (h/day)	Duration	Observations and Remarks	Ref.
		Total	WHO	L>20 µm				
Wistar rats (n=3 / group)	100/475 (475)	912 f/cm^3			-	7 h	<u>475-glass fibres:</u> • No increase in cell proliferation as measured by BRDU uptake (increase with amosite)	Donald-son 1995
Male Fischer rats (n=74 / group)	MMVF 32(E)	38±9 mg/m^3	316±50 f/cm^3	146±28 f/cm^3	6h/d nose-only	5 days + 1 year recovery	<u>E-glass fibres:</u> • Geometric mean dimension: length: 16.1±2.4 µm, diameter: 0.81±1.98 µm • Weighted half-time of fibres longer than **20 µm**: **79 days** (95% CI: 62-96) • 90% clearance of fibres	Hesterberg 1998 (Easter s 2000)

	MMVF 33 (475)	36±8 mg/ m^3	371±55 f/cm^3	163±25 f/cm^3			longer than **20 µm**: **371 days** (95% CI: 272-506) • k_{dis} = 11 ng/cm^2/h <u>475-glass fibres:</u> • Geometric men dimension: length: 16.2±2.3 µm, diameter: 0.74±2.20 µm • Weighted half-time of fibres longer than **20 µm**: **49 days** (95% CI: 40-58) • 90% clearance of fibres longer than **20 µm**: **240 days** (95% CI: 195-300) • k_{dis} = 17 ng/cm^2/h	

4.6.1.3 Repeated dose toxicity: dermal

No data.

4.6.1.4 Repeated dose toxicity: other routes

Intra-peritoneal:

Species	Fibre type	Dose			Injection schedule	Duration of observation	Observations and Remarks	Ref.
		Total	WHO	L>20 µm				
Male C57/B 16 mice (n=3 or 4)	100/475 (475)	-	8.2 x 10^7 f	-	1 x 0.5 ml saline	4 days	• Marked increase in the number of inflammatory cells in the peritoneal cavity 4 days after injection: 14.0 compared to 1.6 million macrophages in control group and 4.58 compared to 0.04 millions of granulocytes in control group.	Davis 1996

Intra-tracheal:

	Fibre type	Dose	Duration of observation	Observations and Remarks	Ref.
Male Wistar rats (n=16)	100/475 (475)	1 x 1 mg	Lung analysis 3 days and 1 year after injection	• Persistence of fibres in the lung: Lung burden (million f. per lung) Fibre length 0.4<l<5 µm 5<l<20µm l>20µm 3 days 2236.8 221.3 8.4 12 mo. 182.4 69.7 2.7 • 1-year clearance of respectively 92, 68 and 68% compared with 96, 84 and 4% for amosite	Davis 1996 Searl 1999

4.6.1.5 Human information

No data.

4.6.1.6 Other relevant information

No data.

4.6.1.7 Summary and discussion of repeated dose toxicity

This endpoint is presented only for information and is not proposed for harmonized classification.

4.6.1.8 Summary and discussion of repeated dose toxicity findings relevant for classification according to DSD

This endpoint is presented only for information and is not proposed for harmonized classification.

4.6.1.9 Comparison with criteria of repeated dose toxicity findings relevant for classification according to DSD

This endpoint is presented only for information and is not proposed for harmonized classification.

4.6.1.10 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification according to DSD

This endpoint is presented only for information and is not proposed for harmonized classification.

4.7 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

No data.

4.8 Germ cell mutagenicity (Mutagenicity)

This endpoint is presented only for information and is not proposed for harmonized classification.

4.8.1 Non-human information

4.8.1.1 In vitro data

Test	Fibre type	Cell system	Protocol	Conc. (mg/l	Observations and Remarks	Ref.
Transfor-mation	JM100 (475)	BALB/c-3T3 cells	72 h	0-1-4-10-38-100 µg/cm^2	• Cytotoxicity at high concentration: around 30% of relative cloning efficiency at 10 µg/cm^2 • Dose-related transformation, significant from 10 µg/cm^2 • Transformed cells exerted anchorage-independent growth (90%)	Gao 1995
Transfor-mation	Code 100 (475)	Syrian hamster embryo cells	-	0.5 µg/cm^2 and above.	• Induction of cell transformation. • Milling of the fibres strongly reduced the effect.	Hester-berg 1984 and 1986
Transfor-mation	Code 100 (475) Code 110 (475)	Syrian hamster embryo cells		0-0.5-0.2-1.5 µg/cm^2 0-3-5-10-20 µg/cm^2	• Statistically significant increase in the transformation frequency at 1.5 µg/cm^2 with code 100 fibre (1.15 µg/cm^2 of fibres results in 1% transformed cell colonies and 62% of survival) • Slight, but not statistically significant or dose-dependent, increase in the transformation frequency with code 110 fibre (larger diameter than code 100).	Mikalsen 1988

Transfor-mation	JM 104/475 (475)	Syrian hamster embryo cells (M3E3/C3)		0-50-100-150 µg/ml	• Significant decrease in cell survival (around 45% of surviving cell at 50 µg/ml and less than 10% at highest doses. • No effect of transformation • Microscopic observation: break of the filamentous structure of the actin system into a granular configuration; complete depolymerisation of the filamentous tubulin system.	Aufder-heide 1994
Micro-nucleus	Code 100 (475)	Syrian hamster embryo cells	-	1 µg/cm^2	• Induction of micronuclei • Milling of the fibres strongly reduced the effect.	Hester-berg 1986
Chromo-somal aberratio ns	Code 100, 104, 108A, 108B (475)	Chinese hamster lung cells		Up to 300 µg/ml	• Fibre samples were crushed and 90% of fibres were < 5 µm long. • Inhibition of colony formation: TD_{50} of 10, 11, 18 and 27 µg/ml, respectively. • No induction of chromosomal aberrations but polyploidy from 10 µg/ml with code 100 and 104 et 100 µg/ml with 108A	Koshi 1991
Micro-nucleus	475 fibres of various diameter s (code 90, 108, 110, 112)	Chinese hamster ovarian cells	48 h	Approx. 25 to 150 x10^4 f/cm^2	• Increased incidence of morphologically abnormal nuclei with little or no loss of viability • Concentration-dependent decrease in proliferation • No significant influence of diameter on toxicity when concentration are expressed as number of fifres/cm²	Hart 1994
Micro-nucleus	JM100 (475)	Chinese hamster lung fibroblast cell line (V79 cells)	24 h	0-10-20-40-80 µg/ml	• Dose-related increase of micronucleated (6.8% at 80 µg/ml) and multinucleated (49.5% at 80 µg/ml) cells. • Significant increase in kinetochore positive micronuclei in cells.	Ong 1997

4.8.1.2 In vivo data

No data.

4.8.2 Human information

No data.

4.8.3 Other relevant information

No data.

4.8.4 Summary and discussion of mutagenicity

This endpoint is presented only for information and is not proposed for harmonized classification.

4.8.5 Comparison with criteria

This endpoint is presented only for information and is not proposed for harmonized classification.

4.8.6 Conclusions on classification and labelling

This endpoint is presented only for information and is not proposed for harmonized classification.

No classification is proposed.

4.9 Carcinogenicity

4.9.1 Non-human information

4.9.1.1 Carcinogenicity: oral

No data.

4.9.1.2 Carcinogenicity: inhalation

Species	**Fibre: type 475**	Conc.			Expo. Time (h/day)	Duration	Observations and Remarks	Ref.
		Total	WHO	L>20 µm				

AH/HAN rats (n=38)	100/475 (475)	5.8 mg/m^3 (estimated)	1119 f/cm^3	137 f/cm^3	7h/d 5d/wk whole-body	12 months lifetime obs.	• After 14 days of exposure: no increase in macrophage and neutrophil levels in the BALF, no increase in cell proliferation at different lung levels but increased level of LDH after 1, 3, 7 or 14 days of exposure. • Raised macrophage number at the end of exposure • No significant lung fibrosis reported (11 animals with very slight fibrosis) • 4 rats (11%) developed benign pulmonary neoplasms. None developed carcinoma nor mesothelioma. • In the control group (n=38), 1 rat (2.6%) developed a pulmonary adenoma and 1 rat a carcinoma. • In the amosite group (n=42), 16 rats (38%) developed a pulmonary tumour and 2 rats (4.7%) a mesothelioma.	Davis 1996 (Miller 1999a) Cullen 1997
Wistar rats (n=24 / sex)	JM100 (475)	5 mg/m^3	332 f/cm^3		5h/d 5d/wk whole-body	12 mo + 4, 7, 12 or 16 mo obs. 24 mo + 4 mo obs.	• Dimensions : 97% < 5µm in length and 43% < 0.1 µm in diameter • No tumours in JM100 and control groups • 9/47 rats (19%) with pulmonary carcinoma in the chrysotile group • No data on survival	Le Bouffant 1984
Rats	JM100 (475)	10 mg/m^3	9625 f/cm^3			24 mo	• Dimensions : 52%>10µm in length and 43%<0.1 µm in diameter • No tumours • No positive or negative control groups	Le Bouffant 1987

Female Wistar rats (n=108)	104/475 (475)	3.0 mg/m^3	252 f/cm^3		5h/d 4d/wk nose-only	12 mo	• Median dimensions: 4.8 µm in length and 0.42 µm in diameter. 90%<12.4µm in length • Lung burden: 0.4 mg after 6 months, 0.6 mg after 12 months and 0.2 mg after 12 additional recovery months. • Half-life about 600 days (vs 200 days for crocidolite). 60% (35% with length>5µm) of the fibres in the lung at the end of exposure were remaining after 12 additional months. • 1/107 pulmonary tumour (1/50 for crocidolite, 0/50 for chrysotile and 0/105 for control groups)	Muhle 1987
Fisher 344 rats (n=50 / sex)	JM100 (475)	10 mg/m^3			7h/d 5d/wk whole-body	12 mo + lifetime obs.	• No data on dimensions • No pulmonary tumours (n=55) in the JM100 group, 3/53 (6%) in the control group and 11/56 (20%) in the chrysotile group.	McCon-nell 1984
F344 rats (n=100)	100/475 (475)	5 mg/m^3	-	-	7h/d 5d/wk whole-body	86 w	• Dimensions: diameter < 3.5 µm; group 3: length > 10 µm and group 4: length < 10 µm • No fibrosis observed • Macrophages aggregates and granulomas resulting in plaque-like foci in pleural and subpleural locations • No mesothelioma or pulmonary tumours reported in the control and exposed groups • Elevated mononuclear cell leukaemia: 35/99 (35.4%, p<0.05) and 42/99 (42.4%, p<0.01) in groups 3 and 4, compared to 21/99 (21.2M) in the control group.	Moor-man 1988

Female Osborne-Mendel rats (n=52-61)	JM100 (475)	2.4 mg/m^3	3000 f/cm^3		6h/d 5d/wk nose-only	24 mo	• Median dimensions : 4.7µm in length (mean=7.5) and 0.45µm in diameter (mean=0.4) • No tumours in JM100 and control groups • 3/57 tumours (5%) in the crocidolite group (1 mesothelioma and 2 carcinomas)	Smith 1987
Fisher 344 rats (n=48)	JM100 (475)	10 mg/m^3	1436 f/cm^3	approx. 108 f/cm^3	7h/d 5d/wk	12 mo expo. + 0 mo, 12 mo or lifetime obs.	• Dimensions : 29% > 10µm in length • Wagner grades of lung fibrosis at 12/16 months and 24 months after the start of exposure was respectively 3.0 and 3.3 for 475-glass and 4.1 and 4.0 for chrysotile. Rats which died spontaneously generally showed a slight increase in the degree of fibrosis seen. • 1/48 rats had a pulmonary adenocarcinoma (2%) in the period 500-1000 days after the start of exposure. 3 had bronchoalveolar hyperplasia. • Controls: no tumour (n=48) • Chrysotile: 11/48 rats (23%) had adenocarcinomas and 5 bronchoalveolar hyperplasia • Inadequate data on survival	Wagner 1984
Male Golden Syrian hamster (n=83)	MMVF 33 (475)	37 mg/m^3	310 f/cm^3	109 f/cm^3	6h/d 5d/wk nose-only	78 wk + 6 wk recovery	• 1 day after a 6 h exposure, lung burden was 11.5x10^5 WHO fibres and 2.2x 10^5 20 µm-length fibres. • No significant increase in lung weight at week 13 and 52 but 20-30% heavier than control at the end of the study. • Cell proliferation at	McConnell 1999 (Hester-berg 1997)

							bronchoalveolar duct junction was increased at weeks 13 (but not after an additional 13-week recovery), 52 and 78. • In the lung, mild excess of macrophages concentrated at bronchoalveolar junctions at week 13 (Wagner grade=2.6). Progression of inflammatory changes accompanied by mild interstitial fibrosis at weeks 26 (Wagner grade=3.5), 52 and 78 (Wagner grade=4.0) • Collagen deposition in the pleura of all animals at 6 and 12 months. This effect is no more statistically significant after 78 weeks exposure + 6 weeks recovery. • After recovery, inflammatory lesions regressed but pulmonary or pleural fibrosis did not. • After 78 weeks, a significant number of fibres were found in diaphragm (995 WHO fibres/mg) and thoracic wall (151 WHO fibres/mg). • 1 hamster (2%) died at 7.5 months and had a mesothelioma with 475-glass exposure. Mesothelial hyperplasia was found in 18 animals (21.7%). • No pulmonary or mesothelial neoplasm in the control group • Amosite induced mesotheliomas: 3/83 (4%) in the low-dose (0.8 mg/m^3), 22/85 (22% in the mid-dose (3.7 mg/m^3) and 17/87 (20%) in the high-dose (7.1 mg/m^3) groups	

Male Syrian golden hamster (60-70)	JM100 (475)	2.4 mg/m^3	3000 f/cm^3		6h/d 5d/wk nose-only	24 mo	• Median dimensions : 4.7 µm in length (mean=7.5) and 0.45 µm in diameter (mean=0.4) • No pulmonary tumours with 475-glass • 1/58 carcinoma in the control group and 0/58 in the crocidolite group.	Smith 1987
Baboons (n=10)	JM 102/104 (102=**475**, 753) (104=**475**, 753, **E**)	1000 f/cm^3				30 mo	• No tumours in exposed and control animals • Peribronchiolar fibrosis in animals exposed to JM 102/104 and crocidolite	Gold-stein 1984
Cynomolgus monkeys (n=12)	100/475 (475)	5 mg/m^3	-	-	7h/d 5d/wk whole-body	18 mo (=72 weeks)	• Dimensions: diameter < 3.5 µm; group 3: length > 10 µm and group 4: length < 10 µm • No changes in pulmonary function parameters • Macrophages aggregates in lung and tracheobronchial lymph nodes • No mesothelioma or pulmonary tumours reported	Moor-man 1988

4.9.1.3 Carcinogenicity: intraperitoneal

Species	Fibre type	Dose			Injection schedule	Duration of observa-tion	Observations and Remarks	Ref.
		Total	WHO	L>20 µm				

Female Wistar rats (n=44)	JM104/E (E) JM 475 (475)	2 or 10 mg 2 mg	-	-	2 or 10 mg 2 mg	lifetime	• E-glass: 14/44 (32%) and 29/44 (66%) rats with abdominal tumours at doses of 2 and 10 mg, respectively • 475-glass: 2/44 (4%) rats with abdominal tumours (dimensions: median length=10 µm and median diameter=0.2 µm) • Chrysotile: 9/44 (20%), 26/44 (59%) and 35/44 (79%) rats with abdominal tumours at doses of 0.4, 2 and 10 mg, respectively	Pott 1984
Male Wistar rats (n=24)	100/475 (475)	8,3 mg	1868 $x10^6$ f	9 $x10^6$ f	1 x 8,3 mg (in 2 ml saline)	lifetime	• Mean diameter: 0.32 µm • 8/24 animals (33%) developed mesothelioma, compared to 21/24 (88%) with amosite. • No negative control	Davis 1996 (Miller 1999b)
Female Osborne-Mendel rats	JM 100 (475)	25 mg			1x25 mg in 0.5 mL saline	lifetime	• Dimensions: median length: 4.7 µm and median diameter: 0.4 µm • Mesotheliomas in 8/25 JM100-treated rats (32%), 20/25 crocidolite-treated rats (80%) and 0/150 control rats	Smith 1987
Female Sprague-Dawley rats	104/475 (475)	2 -10 mg			1 injection (in 2 ml saline)	lifetime	• Dimensions: median length=2.4 µm and median diameter=0.33 µm • Sarcomas, mesotheliomas and carcinomas were seen in 21/54 (39%) and 24/53 (45%) animals treated with 2 and 10 mg, respectively • Control: 3/54 animals (5.5%) had tumours	Pott 1987

Female Wistar rats	104/475 (475)	0.5 – 2 mg			1 x 0.5 or 2 mg	lifetime	• Dimensions: median length=3.2 µm and median diameter=0.18 µm • 5/30 (17%) and 8/31 (26%) animals treated with 0.5 or 2 mg had abdominal tumours • Crocidolite: 18/32 (56%) and 28/32 (87%) rats with abdominal tumours at doses of 0.5 and 2 mg, respectively • Saline-control group: 2/32 rats (6%) had tumours	Pott 1987
Female Wistar rats	JM 475 (475)	5 mg	680 x10^6 f			130 weeks	• Dimensions: median length=2.6 µm and median diameter=0.15 µm • 34/53 treated rats (64%) had tumours (excluding uterine tumours) and 2/102 control rats (2%) had mesotheliomas	Pott 1989
Female Wistar rats (n=46-48)	JM 475 (475)	-	0.33 x10^9 f	-			• 17 of treated rats (36%) developed abdominal tumours • Control (saline): 2/50 had tumours	Pott 1991
Female Wistar rats	JM104 (475, 753, E)				2, 10 or 2x25 mg	lifetime	• Dimensions: median length=10 µm and median diameter=0.2 µm • 2 mg-dose: 17 rats had mesothelioma, 3 a sarcoma (n=37). Total tumour rate: 27.4% • 10 mg-dose: 36 rats had mesothelioma, 4 a sarcoma and 1 a carcinoma (n=77). Total tumour rate: 53.2% • 2x25 mg-dose: 47 rats had mesothelioma, 8 a sarcoma (n=77). Total tumour rate: 71.4% • crocidolite group (2 mg): 15/39 abdominal tumours	Pott 1976

							(38%)	
Rats	JM106 (475, 753, E)				2, 10 or 4x25 mg	lifetime	• Dimensions: median length=3 µm and median diameter=0.4 µm • 2 mg-dose: 1 rat had a mesothelioma (n=34). Total tumour rate: 2.9% • 10 mg-dose: 2 rats had mesothelioma, 2 a sarcoma (n=36). Total tumour rate: 11.0% • 4x25 mg-dose: 20 rats had mesothelioma, 3 a sarcoma (n=32). Total tumour rate: 72%	Pott 1976

4.9.1.4 Carcinogenicity: intratracheal

Species	Fibre type	Dose			Injection schedule	Duration of observation	Observations and Remarks	Ref.
		Total	WHO	L>20 µm				
Female Wistar rats	104/475 (475)	10 mg			20 x 0.5 mg in 0.3 mL saline	Lifetime	• Dimensions: median length=3.2 µm and median diameter=0.18 µm • Lung tumours in 5/34 (15%) treated animals (1 adenoma and 4 carcinomas) • 0/40 in control animals • 15/35 in the crocidolite group (43%)	Pott 1987
Female Osborne-Mendel rats (n=22)	JM100 (475)	10 mg			5 x of 2 mg in 0.2 mL saline (weekly)	Lifetime	• Dimensions: mean length=4.7 µm and mean diameter=0.4 µm; 19% > 10µm in length • No tumour in controls and JM100-treated animals • 2/25 in crocidolite-treated animals (8%)	Smith 1987

Syrian golden hamster (n=35 / sex)	JM 104 (475, 753, E)	26 mg			26 x 1mg in 0.2 mL 0.005% gelatine in saline (every 2 wk for 52 wk)	85 wk	• Dimensions: 58% < 5 µm in length, 88%< 1.0 µm in diameter • No mesothelioma or pulmonary tumour in JM104- or crocidolite-treated groups	Feron 1985
Male Syrian golden hamster	JM 104 (475, 753, E)	8 mg			8 x 1mg in 0.15 mL saline (weekly)	113 wk	• Group with median length= 7 µm: 48/136 animals (35%) developed a tumour (5 lung carcinomas, 37 mesotheliomas, 6 sarcomas) • Group with median length= 4.2 µm: 38/138 animals (27%) developed a tumour (6 lung carcinomas, 26 mesotheliomas, 6 sarcomas) • Crocidolite: 18/42 rats (13%) had a tumour (9 lung carcinomas, 8 mesotheliomas, 1 sarcomas) • Control (TiO_2): 2/135 rats (1.5%) had sarcoma	Mohr 1984

4.9.1.5 Carcinogenicity: intrapleural

Species	Fibre type	Dose			Injection schedule	Duration of observation	Observations and Remarks	Ref.
		Total	WHO	L>20 µm				

Sprague Dawley rats (n=32-45)	JM 104 (475, 753, E)	20 mg			1 x 20 mg in 2 mL saline	Lifetime	• Dimensions: mean length=5.89 µm and mean diameter=0.229 µm • 6/45 animals (13%) had mesothelioma. • Chrysotile : 14/33 (42%), and crocidolite: 21/39 (54%) mesotheliomas • No thoracic tumours in 32 control animals.	Monchaux 1981
Sprague Dawley rats (n=48)	JM100 (475)	20 mg	30.2 x10^8 f		1 x 20 mg in 0.5 mL saline	Lifetime	• Dimensions: 88% < 5 µm in length and 98.5% ≤ 1 µm in diameter • 4/48 treated animals (8%) and 0/24 control animals had **mesothelioma** • Chrysotile: 6/48 mesotheliomas (12%)	Wagner 1984
Female Fisher rats (n=25)	JM100 (475)	20 mg			1 x 20 mg	2 to 430 days	• Dimensions: mean length=2.2 µm and mean diameter=0.15 µm • Chronic inflammation occurred in 9 rats (37.5%), fibrosis in 18 rats (75%), foreign body reaction in 10 rats (41.6%), mesothelial dysplasia in 9 (37.5%) and hyperplasia in 16 rats (66.6%). • 3 animals (12.5%) killed at day 102, 408 and 416 days after inoculation had mesothelioma	Fraire 1994
Wistar rats (n=16 / sex)	JM100 (475)	20 mg			1 x 20 mg in 0.4 mL saline	Lifetime	• Dimensions: mean length=1.7 µm and mean diameter=0.12 µm. 99% < 0.5 µm in diameter and 2%> 20 µm in length • 4/32 treated animals (12.5%) had mesothelioma, 0/32 in the control group.	Wagner 1976

4.9.1.6 Carcinogenicity: dermal

No data.

4.9.2 Human information

Study type	Fibre type	End point	Population	Exposure assessment	Observations and Remarks	Ref.
Case-control	Microfibres	Larynx and hypopharynx cancers	Patients recruited from 15 hospitals in 6 French cities. Larynx cancers: n=296 subjects Hypopharynx cancers: n=201 subjects Controls: n=295 with non-respiratory cancers	Job history was collected by face to face interview. Exposure was assessed using a job-exposure matrix and 2 categories were defined: Ever exposed or Never exposed	• Results adjusted for age, smoking and alcohol consumption • Laryngeal cancers: 16 cases/9 controls ever exposed; OR=1.28 (95% CI: 0.51-3.22) • Hypopharynx cancers: 7 cases/9 controls ever exposed; OR=0.78 (95% CI: 0.26-2.38) • No significant association between laryngeal or hypopharyngeal cancers and exposure to microfibres but exposure concerned only a few subjects.	Marchand 2000
Historical cohort	Fibre glass including 2/10 plants producing special-application glass fibres	Respira-tory system cancers	32,110 production or maintenance workers employed for 1 year or more between 1945 and 1992. Control: US or local county mortality rates	Quantitative estimation of fibre exposure.	• No evidence of excess mortality risks for all causes of death, all cancer death or non malignant respiratory disease mortality. • General cohort: a 6% (SMR=1.06, 95% CI: 1.00-1.14, p=0.05) and 16% (SMR=1.16, 95% CI: 1.08-1.24, p<0.01) excess of respiratory system cancer mortality was observed compared to respectively local and national rates. • Duration of exposure and cumulative exposure were not associated with an increased risk of respiratory system cancer. • Possible co-exposure to arsenic, asbestos, asphalt, epoxy, formaldehyde, PAH,	Marsh 2001 (IARC 2002)

					phenolics, silica, styrene and urea. • Special-purpose glass fibres exposure category: SMR=1.09, 95% CI: 0.87-1.36 (n=81 cases)	

4.9.3 Other relevant information

Test	Fibre type	Cell system	Protocol	Conc. (mg/l)	Observations and Remarks	Ref.
Cyto-toxicity	JM100 (475)	Rat alveolar macrophages	24, 48 or 72h.	0-100-200-300 µg/ml	• Cell viability (trypan blue exclusion): dose-related decrease of cell viability at all doses and time points. • Membrane integrity: significant dose-dependent increase of LDH and β-gal release • Macrophage function: significant dose-dependent decrease of Zymosan-stimulated oxygen and hydrogen peroxide consumption.	Castra-nova 1996
Cyto-toxicity	JM100 (475)	Rat alveolar macrophages	18 h	0-50-100-250-500 µg/ml	• Macrophage function: chemiluminescence (measure of superoxide release) was significantly decreased at 250 and 500 µg/ml. • Macrophage cytotoxicity: LDH release was significantly increased at 250 and 500 µg/ml. • Longer fibres (mean length of 17 and 33 µm) appear to be more toxic	Blake 1998
Cell activation	JM100 (475)	A549 cells	20 h	0-5-10-15-25-50 µg/ml	• Marked dose-dependent cytotoxicity • No change in the expression of p53, Cip1 and Gadd153 proteins (proteins associated with DNA damage). Increase with IUCC crocidolite.	Johnson 1997

Cell activation	100/475 (475) 104E (E)	Rat alveolar macrophages	24 h	8.2 x 10^6 fibres (WHO)	• Both microfibres showed an intermediate activity with a TNF-α production of 60 (475-glass) and 71 (E-glass) TNF-α unit/10^6 cells. Two silicon carbide whiskers and two asbestos samples were more active while RCF and other MMVF tested were inactive.	Cullen 1997
Cell activation	Code 100 (475)	Rat alveolar macrophages Hamster tracheal epithelial cells	1 h 3 h	2.5 to 25 µg/cm^2 0.1 to 20 µg/cm^2	• Inflammatory capability: significant dose-related increases of superoxide anions release from 5 µg/cm^2 • Membrane integrity: significant dose-related increases of ^{15}Cr release from 1 µg/cm^2	Moss-man 1990
Cell activation	100/475 (475)	Hamster and rat alveolar macrophages		2.5 µg/ml or 5 µg/cm^2	• Induction of superoxide anions release	Hansen 1987
Cell activation	JM100 (475)	Rat alveolar macrophages		3 x 10^7 f/ml	• Inhibition of the superoxide anions release by both naked or IgG-coated fibres	Brown 1998
Cell activation	JM100 (475)	Mouse monocyte macrophage cell line RAW 264.7		3.0 x 10^8 2.0 x 10^7 f/ml	• Production of TNF-α factor and activation of transcription factor • Effects were more important with longer fibres (17 µm) than with shorter fibres (7µm)	Ye 1999
Cell activation	100/475 (475)	Rat alveolar macrophages, human blood monocytes, THP-1 human macrophages cell line, mouse macrophage cell line		3 x 10^7 f/ml	• No significant increase of TNF-α release	Fisher 2000

4.9.4 Summary and discussion of carcinogenicity

In comparable experimental conditions to those of E-glass fibres, 475-glass fibres induced by **inhalation** in rats few benign pulmonary tumours only (Davis 96). This result confirms previous experiments in which no significant increase of the tumour incidence with exposure to 475-glass was observed. However, several important limits were identified in these studies: insufficient exposure duration (Le Bouffant 84, Muhle 87, Moorman 88, Wagner 84), use of short fibres samples (Le Bouffant 84, Muhle 87, Smith 87), no data on fibre dimensions (McConnell 84), no positive asbestos control group (Le Bouffant 87, Moorman 88), no data on animal survival (Le Bouffant 84, Wagner 84). The absence of a significant induction of tumours with asbestos in Muhle 87 and Smith 87 strongly questions the relevance of these studies in the present evaluation.

In hamster studies, Smith (87) observed no tumour in animals exposed to both 475-glass or crocidolite. In the recent study by McConnell (99) with a 18-month exposure, 1 hamster (2%) had a mesothelioma. It was accompanied by pleural fibrosis and mesothelial hyperplasia in 22% of the animals.

Two **inhalation** studies were performed on monkeys. No tumours were reported after respectively 18 months (Moorman, 88) and 30 months (Goldstein, 84) of exposure and animals were sacrificed at the end of the exposure. Longer exposures and observations would have been required to detect neoplasms in such animals.

Several studies are available on rats by the **intraperitoneal (IP) route for 475-glass fibre**. In all studies, an increased incidence of abdominal tumours, mesotheliomas, sarcomas and lung carcinomas was observed (Pott 1976, 1984, 1987, 1989, 1991, Davis 1996, Miller 1999b, Smith 1987). When two levels of dose are used, a positive trend between tumour incidence and exposure is observed (Pott 76, Pott 84, Pott 87). It should however be noted that the type of glass (475, E or 753) is not indicated in Pott 76.

One study on 475-glass fibre did not report increased incidences of lung tumours following **intratracheal instillation** fibres in rat (Smith 87) but in these studies, the crocidolite control-groups were also negative. Two other studies reported lung tumours in 15% of animals in rats (Pott 87) and 27% or 35% of the animals in hamster (Mohr 84) with an increased incidence with longer fibres. It should also be noted that the type of glass (475, E or 753) is not indicated in the hamster studies.

Following massive **intrapleural injection** of **475-glass fibres**, mesotheliomas were consistently reported in 8 to 12% of the animals in three different rat studies (Wagner 84, Fraire 94, Wagner 76). In Fraire 94, fibrosis was also observed in 75% of animals and mesothelial hyperplasia in 66%.

Classification by IARC in 2001:

In its evaluation, IARC concluded that there is sufficient evidence in experimental animals for special-purpose glass fibres including E-glass and 475-glass fibres and classified them as possibly carcinogenic to humans (group 2B), as for refractory ceramic fibres.

Human data for the both fibres:

A case-control study did not show any association between laryngeal or hypopharyngeal cancers and microfibre exposure (Marchand 2000) but the study included a very small number of microfibre-exposed subjects. In an historical cohort study (Marsh 2001), an excess of respiratory cancer was observed in the general fibre glass group but not in the special–purpose glass fibres sub-group. The size of this sub-group was also limited. Overall, these data are not considered sufficient to draw any conclusion on the potential carcinogenic effects in humans.

4.9.5 Comparison with criteria

The **epidemiological data** do not bring sufficient evidence of carcinogenicity in human.

For experimental data, the CLP criteria for classification establish different levels of evidence:
— *"**sufficient evidence of carcinogenicity**: a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence. A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites;*
— ***limited evidence of carcinogenicity**: the data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs."*

Experimental data for 475-glass fibres clearly provide evidence of a carcinogenic effect in several species (rats, hamsters and monkeys) and in both sexes in numerous independent studies in different laboratories. Tumours consist in both benign and malignant lung tumours (carcinomas, mesotheliomas and sarcomas) and abdominal tumours by different routes of exposure (inhalation, intraperitoneal, intratracheal and intrapleural).

Indeed, special-purpose fibres show a carcinogenic potential by the intraperitoneal (E and 475), intratracheal (data on 475 only) and intrapleural (data on 475 only) routes. Fibre biopersistency may enable their migration further inhalation into the pleural cavity and emphasise the relevance of positive results by the intrapleural route.

Although carcinogenicity potential is confirmed by inhalation in a well-designed study with E-glass fibre, no study clearly demonstrates the induction of tumour following inhalation of 475-glass fibres and most of the available studies show important limitations.

On the basis of animal studies by inhalation, E-glass fibres induce marked macrophage reaction, alveolar fibrosis and hyperplasia which may indicate a progressive pathway to neoplastic transformation of respiratory cells whereas 475-glass fibres do not exhibit such effects by inhalation (Cullen, 2000). Besides, comparison between the carcinogenic potential of both fibres by intraperitoneal route (Pott 1984) shows that 32% of rats has abdominal tumours with E-glass although only 4% of rats has abdominal tumours with 475-glass tumours.

4.9.6 Conclusions on classification and labelling

Overall, largely based on animal evidence, E-glass fibres are presumed to have carcinogenic potential for humans whereas 475-glass fibres are suspected to be human carcinogens.

Because the danger comes from the inhalation exposure, the not breathable fibres are not concerned by this classification and as mentioned in the specific entry, only the fibres with a diameter inferior to 3 µm are concerned thus the note R do not apply.

A classification Carc. 2; H351 is therefore warranted for 475-glass fibre (Carc. Cat. 3 – R40 according to the DSD).

4.10 Toxicity for reproduction

No data.

4.11 Other effects

No data.

4.11.1 Non-human information

No data.

5 ENVIRONMENTAL HAZARD ASSESSMENT

Not relevant for this dossier.

6 OTHER INFORMATION

Not relevant.

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8 ANNEXES

Discussions at the TC C&L:

Summary records – TC C&L November 2005 (doc ECBI/60/05 Rev. 3)

In **November 2005** a preliminary discussion took place.

Discussion of this substance was introduced by France, which reported that special purpose fibres were incorrectly regarded in the same Annex I entry as mineral wool. In fact they should be in the same entry as refractory ceramic fibres as a result of their known carcinogenicity. The French proposal was for a classification of special purpose fibres as Carc. Cat.2; R45.

Industry spoke to their paper (Add 1). They argued that special purpose fibres fell into two broad sub-Groups one of which (E glass) should be classified as a category 2 carcinogen. However the second sub-Group (identified as 475) did not have the same properties and should be considered as a category 3 carcinogen.

In the course of discussion member states raised a number of concerns. France drew attention to the difficulty of inhalation studies as a valid test for eliminating concerns over the carcinogenicity of fibres. Germany pointed out the importance of IP studies. The United Kingdom asked for further information, particularly the arguments that observations of mesothelioma in hamsters were not relevant to humans.

Industry promised to provide further information, particularly the relationship between inhalation and IP studies. The Chair said the discussion would be taken up again at the next meeting.

Summary records – TC C&L Mars 2006 (doc ECBI/90/06 Rev. 8)

ECBI/10/05	F, classification proposal.
ECBI/10/05 Add. 1, 2,3,4	IND, respose to proposal

In **November 2005** a preliminary discussion took place and industry promised to provide further information on a number of issues.

Carcinogenicity

The Chair introduced this substance by reporting that industry said it preferred to keep the existing Annex 1 entry with the Carc Cat 3 classification. France was invited to react to the industry comments on their proposal.

France reported that it maintained the view that the existing classification was unsatisfactory. The fibres covered by the entry are persistent with a half-life similar to E glass. This suggested similar properties and it was appropriate to classify both special purpose fibres and E glass as a Carcinogen Category 2.

In responding to these comments Industry said the database on the substance had not changed since the original classification. There was no statistical difference in the frequency of adenocarcinomas and there was an absence of fibrosis. Bio-persistence was not a valid inclusion criterion for

carcinogenicity; it had only been used in the past to enable exoneration. The only valid data were the complex inhalation studies which had been carried out prior to the 1977 classification decision.

During the subsequent discussion the United Kingdom indicated that they preferred keeping the original Carc. Cat 3 classification. However other Member States noted the confusion in relation to the description of the substance in the current entry which appeared to include E glass for which there was good evidence for Carc Cat 2. This led Germany and the Netherlands to suggest that a split entry might be appropriate. However they acknowledged there would be difficulties in developing a suitable characterisation of the substance.

Conclusion:

In drawing the discussion to a close the Chair suggested Member States needed to reflect on the issue. There appeared to be three possibilities; to maintain the status quo, to adopt the French proposal, or to develop split entries. Industry commented that the latter option would be extremely difficult to introduce.

Summary records – TC C&L October 2006 (doc ECBI/13/07 Rev. 2)

ECBI/10/05	F, classification proposal.
ECBI/10/05 Add. 1, 2, 3, 4	IND, response to proposal
ECBI/10/05 Add. 5	IND, summary of chemistry and key toxicological issues

In **November 2005** a preliminary discussion took place and industry promised to provide further information on a number of issues.

In **March 2006**, it was agreed to delete the Xi; R38 classification for both entries 650-016-00-2 (including CAS number 65997-17-3) and 650-017-00-8. The Chair suggested Member States needed to reflect on the carcinogenicity issue. There appeared to be three possibilities; to maintain the status quo, to adopt the French proposal, or to develop split entries. Industry commented that the latter option would be extremely difficult to introduce.*Carcinogenicity:*

ECB summarised the conclusions from the last meeting. Re-classification was needed for E-glass fibres. IND had sent additional information on 'E-glass' and 'Type 475 special purpose fibres' and wanted them to be considered as different. Epidemiology data did not warrant a Carc. Cat. 2 classification for the Type 475 fibres, according to IND. There was no significant fibrosis in the Cullen study, therefore no carcinogenicity classification warranted. A further paper was published the week prior the meeting and would be distributed to the TC C&L during the Follow-up period. The Type 475 special purpose fibres should be classified with Carc. Cat. 3, according to IND.

ECB said at the last meeting there were split opinions between Carc. Cat. 3 and Carc. Cat. 2. We had a discussion to split the fibres amongst 2 entries.

F commented on the bio-persistence and bio-availability. The two types of fibres had different composition. The 'Type 475 special purpose fibres' and 'E-glass fibres' had different dissolution rates. Both fibres could be grouped on this basis and no split entry was needed. The E-glass fibres induced fibrosis. Also very slight fibrosis was found with 'Type 475 special purpose fibres' at short exposure. For F this was enough evidence for Carc. Cat. 2, for both fibre categories.

NL asked said that they had looked at dissolution rate and then at fibrosis, but they did not see the relation between dissolution rates and the category.

IND said the dissolution rate is an interesting concept. When developed, nobody felt that this could be used for C&L purposes. It was an indication of a relative category of where the fibres belong. The difference between Carc. Cat. 2 and Carc, Cat. 3, however, must be determined by

toxicological studies. In this case the inhalation study was negative. There was also not significant fibrosis. Therefore we need different categories for 'Type 475 special purpose fibres' and 'E-glass fibres'.

UK agreed with IND that the two fibre types are different. Thus Carc. Cat. 3 for 'Type 475 special purpose fibres'. NL also agreed to this.

DE said there was a different potency between the fibres. However, also 'Type 475 special purpose fibres' could still be classified as Carc. Cat. 2. A practical problem was also how to present the classification in Annex I because both fibres had the same CAS number. F confirmed the CAS number covers many fibres.

ECB summarised the TC C&L agreed to classify the 'Type 475 special purpose fibres' in Cat. 3. IND was asked to provide the chemical identification for both entries in the Follow up procedure. The TC C&L agreed to classify the 'Type 475 special purpose fibres' in Carc. Cat. 3 and the E-glass fibres in Carc. Cat. 2, and the only remaining issue was then how to identify the substances in the two different entries.

IND confirmed that they would provide further information in the Follow up procedure.

F asked IND what the percentage of oxide was in the fibres. IND responded: greater than 18 % but close to the limit.

Conclusion:

The TC C&L agreed to classify 'Type 475 Special purpose fibres' with Carc. Cat. 3; R40 while 'E-glass fibres' would remain with the current Carc. Cat. 2; R49 classification.

Follow-up:

IND sent in ECBI/10/05 Add. 6 for identification of the substances to be covered by the two entries.

F proposed to define following four entries for fibres:

- To keep the current entries Index 650-017-00-8 and Index 650-016-00-2 as they are.

- To create one additional entry for E-fibres (with a new index number) and one additional entry for 475-fibres (which will differ from index 650-016-00-2 by the absence of nota Q).

Follow-up conclusion:

The definition of the new entries should be confirmed at the March 2007 meeting.

Follow-up III of TC C&L October 2006 (doc ECBI/09/07)

IND sent in ECBI/10/05 Add. 6 for identification of the substances to be covered by the two entries.

Member States were invited to react in case they did not agree with the entries as identified.

FR: The current index 650-017-00-8 also covers refractory ceramic fibres (RCF) and should therefore not be restricted to E-fibres.

Besides, the current index 650-016-00-2 which is classified Carc. Cat. 3; R40 and could apply by default to 475-type fibres, is specific because of nota Q which allows exemption of the carcinogenic classification under certain circumstances.

For these reasons, we propose to have the following entries:

- To keep the current entries Index 650-017-00-8 and Index 650-016-00-2 as they are.

- To create one additional entry for E-fibres (with a new index number) and one additional entry for 475-fibres (which will differ from index 650-016-00-2 by the absence of nota Q).

Besides, the chemical composition of the glass may not be sufficient to characterise appropriately the entries. To our knowledge, E-glass may also be used in other type of glass fibres than special purpose fibres, such as continuous glass filaments for example. Therefore, an appropriate way to identify the entries could be to specify both composition and size and to limit the entries to fibres with a mean diameter of less than 3 µm.

IND sent documents ECBI/10/05 Add. 8 parts I, II and III. The values of the type 475 fibres are corrected in correspondence with the table of document 10/05 Add. 8 part II.

MS were asked to react in written in case they do not agree to the new IND proposal prior 31 August 2007. In case no reactions no further detailed discussion is foreseen to take place at the September meeting, but the entry as defined here can be considered confirmed.

No further comments were received.

Final Conclusion:

TC C&L has then confirmed the entry as written here, and there will be no further discussion.

After FUII:

ECB: The CAS No 65997-17-3 is coupled to EC No 266-046-0 with the substance name *Glass, oxide, chemicals* and a description starting with '"This category encompasses the various chemical substances manufactured in the production of inorganic glasses……..". Whether the CAS and EC Numbers should be assigned to the more specified entry *Type 475 Special purpose fibres* still has to be decided before this entry is included in the next ATP.