CLH report

Proposal for Harmonised Classification and Labelling

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

Substance Name: E-glass special purpose fibres

EC Number: **Not assigned**

CAS Number: **Not assigned**

Index Number: **Not assigned**

Contact details for dossier submitter: ANSES (on behalf of the French MSCA)

253 avenue du General Leclerc

F-94701 Maisons-Alfort Cedex

+33 1 56 29 19 30

reach@anses.fr

Version number: 2 **Date: February 2013**

CONTENTS

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING 4

1.1 SUBSTANCE 4
1.2 HARMONISED CLASSIFICATION AND LABELLING PROPOSAL 4
* THE TEXT OF THE NOTES IS GIVEN IN SECTION 2.1 OF THE CLH REPORT 4
1.3 PROPOSED HARMONISED CLASSIFICATION AND LABELLING BASED ON CLP REGULATION AND/OR DSD CRITERIA 5

2 BACKGROUND TO THE CLH PROPOSAL 9

2.1 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING 9
2.2 SHORT SUMMARY OF THE SCIENTIFIC JUSTIFICATION FOR THE CLH PROPOSAL 11
2.3 CURRENT HARMONISED CLASSIFICATION AND LABELLING 11
2.4 CURRENT SELF-CLASSIFICATION AND LABELLING 12
2.4.1 Current self-classification and labelling based on the CLP Regulation criteria 12
2.4.2 Current self-classification and labelling based on DSD criteria 12

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL 12

SCIENTIFIC EVALUATION OF THE DATA 13

1 IDENTITY OF THE SUBSTANCE 13

1.1 NAME AND OTHER IDENTIFIERS OF THE SUBSTANCE 13
1.2 COMPOSITION OF THE SUBSTANCE 15
1.2.1 Composition of test material 16
1.3 PHYSICO-CHEMICAL PROPERTIES 16

2 MANUFACTURE AND USES 17

2.1 MANUFACTURE 17
2.2 IDENTIFIED USES 18

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES 18

4 HUMAN HEALTH HAZARD ASSESSMENT 18

4.1 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION) 18
4.2 ACUTE TOXICITY 18
4.3 SPECIFIC TARGET ORGAN TOXICITY – SINGLE EXPOSURE (STOT SE) 18
4.4 IRRITATION 18
4.4.1 Skin irritation 18
4.4.2 Respiratory tract irritation 19
4.5 CORROSIVITY 19
4.6 SENSITISATION 19
4.7 REPEATED DOSE TOXICITY (INCLUDING BIOPERSISTENCY) 19
4.7.1 Non-human information 19
4.7.1.1 Repeated dose toxicity: oral 19
4.7.1.2 Repeated dose toxicity: inhalation 19
4.7.1.3 Repeated dose toxicity: dermal 20
4.7.1.4 Repeated dose toxicity: other routes 20
4.7.1.5 Human information 20
4.7.1.6 Other relevant information 21
4.7.1.7 Summary and discussion of repeated dose toxicity 21
4.7.1.8 Summary and discussion of repeated dose toxicity findings relevant for classification according to DSD 21
4.7.1.9 Comparison with criteria of repeated dose toxicity findings relevant for classification according to DSD 21
4.7.1.10 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification according to DSD 21

4.8 SPECIFIC TARGET ORGAN TOXICITY (CLP REGULATION) – REPEATED EXPOSURE (STOT RE) 21
4.9 GERM CELL MUTAGENICITY (MUTAGENICITY) 21
4.10 CARCINOGENICITY 21
4.10.1 Non-human information *21*
4.10.1.1 Carcinogenicity: oral 21
4.10.1.2 Carcinogenicity: inhalation 21
4.10.1.3 Carcinogenicity: intraperitoneal 22
4.10.1.4 Carcinogenicity: intra-tracheal 24
4.10.1.5 Carcinogenicity: intra-pleural 25
4.10.1.6 Carcinogenicity: dermal 25
4.10.2 Human information *26*
4.10.3 Other relevant information *27*
4.10.4 Summary and discussion of carcinogenicity *27*
4.10.5 Comparison with criteria *28*
4.10.6 Conclusions on classification and labelling *29*
4.11 TOXICITY FOR REPRODUCTION 29
4.12 OTHER EFFECTS 29
5 ENVIRONMENTAL HAZARD ASSESSMENT 29
6 OTHER INFORMATION 29
7 REFERENCES 29
8 ANNEXES 33

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	E-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. 1B – H350i (with note R)	Carc. Cat. 2 ; R49 (with note R)
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Carc. 1B – H350i (with note R)	Carc. Cat. 2 ; R49 (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. 1B – H350i		Carc. 1B – H350i	
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 – repeated exposure	None		None	Not evaluated
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: "Danger"
Hazard statements: H350i
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.2; R49		Carc. Cat.2; R49	
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: T
R-phrases: R49
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 E-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 E-glass fibres, the current index number 650-016-00-2 currently applies.

In this proposal for harmonised classification, E-glass special purpose fibres are proposed to be classified as Carc. 1B – H350i and the classification assigned to the entry with index number 650-016-00-2 is therefore not appropriate (Carc. 2 – H351). A separate entry for the E-glass fibres is proposed.

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 E.

There are two registration dossiers on E-glass fibres and they have been taken into account for the completion of this CLH report (identity of the substance).

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 E-glass special purpose 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 E-glass special purpose fiber. E-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 E-glass fibres.

To our knowledge, E-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 E-glass fibres [Calcium-aluminium-silicate fibres with random orientation with the following composition (% given by weight): SiO_2 50.0-56.0%, Al_2O_3 13.0-16.0%, B_2O_3 5.8-10.0%, Na_2O <0.6%, K_2O <0.4%, CaO 15.0-24.0%, MgO <5.5%, Fe_2O_3 <0.5%, 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 E-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 fibers (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 E-glass special fibers. The available data as shown in this dossier demonstrate the carcinogenic potential of these fibers 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 E-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 the E-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, E-glass special-purpose fibres show a carcinogenic potential by the intraperitoneal route and by inhalation in a well-designed study.

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. 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.

2.3 Current harmonised classification and labelling

According to their chemical composition, E-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

2.4.1 Current self-classification and labelling based on the CLP Regulation criteria

There are two registration dossiers on E-glass fibres. They both classify E-glass fibres in carcinogenicity 1B by inhalation.

It is noted that in the classification given by manufacturers and importers in the registration dossiers, the classifications for carcinogenicity differ between registrants, illustrating the current potential misinterpretation of the existing harmonised entries and most differ with the proposed harmonized classification.

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 E-glass special purpose fibers in the CLH inventory.

2.4.2 Current self-classification and labelling based on DSD criteria

See above.

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

E-glass special purpose 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

E-glass is a member of the family calcium-aluminium-silicate glasses. Boron oxide is generally a major additive of E-glass. E-glass special purpose fibres are E-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 E 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 E-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)

Chemical composition of E-glass fibres, according to the registration dossier and communicated to the TC C&L (in the document ECBI/10/05/ Add.6):

Oxides	(Weight %)
SiO_2	50.0-56.0%
Al_2O_3	13.0-16.0%
B_2O_3	5.8-10.0%
Na_2O	<0.6%
K_2O	<0.4%
CaO	15.0-24.0%
MgO	<5.5%
Fe_2O_3	<0.5%
ZnO	-
BaO	-
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:	Glass, oxide, chemicals[2]
IUPAC name:	IUPAC name not allocated
CLP Annex VI Index number:	[2]
Molecular formula:	Not applicable (a generic molecular formula cannot be provided for E-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
E-glass special purpose fibres	Ca 100%	-	-

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

Table 7: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
None	-	-	-

[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 fiber but correspond to a wide range of fibres.

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	ca. 800 °C	GE Healthcare, 2010	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.

Secondary filters HEPA in vacuum cleaners and high-efficiency filtration of the air in residential buildings.

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 available.

4.2 Acute toxicity

No data available.

4.3 Specific target organ toxicity – single exposure (STOT SE)

No data available.

4.4 Irritation

4.4.1 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.

4.4.2 Respiratory tract irritation

No data available.

4.5 Corrosivity

No data available.

4.6 Sensitisation

No data available.

4.7 Repeated dose toxicity (including biopersistency)

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

4.7.1 Non-human information

4.7.1.1 Repeated dose toxicity: oral

No data available.

4.7.1.2 Repeated dose toxicity: inhalation

Species	Fibre type	Conc.			Expo. time (h/day)	Duration	Observations and Remarks	Ref.
		Total	WHO	L>20 µm				
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:</u> • Geometric mean dimension: length: 16.1±2.4 µm, diameter: 0.81±1.98 µm • Weighted half-time of fibres longer than 20µm: 79 days (95% CI: 62-96) • 90% clearance of fibres longer than 20µm: 371days (95% CI: 272-506) • k_{dis} = 11 ng/cm^2/h <u>475-glass:</u>	Hesterberg 1998 (Eastes 2000)
	MMVF 33 (475)	36±8 mg/m^3	371±55 f/cm^3	163±25 f/cm^3				

							• Geometric men dimension: length: 16.2±2.3 µm, diameter: 0.74±2.20 µm • Weighted half-time of fibres longer than 20µm: 49 days (95% CI: 40-58) • 90% clearance of fibres longer than 20µm: 240 days (95% CI: 195-300) • k_{dis} = 17 ng/cm^2/h	
Male Wistar rats	E-glass	2.4 mg/m^3 7.0 mg/m^3 17.3 mg/m^3	197.9 f/cm^3 623.1 f/cm^3 1886.5 f/cm^3	16.8 f/cm^3 50.9 f/cm^3 142.3 f/cm^3	6h/d 5d/wk	3 months + 3 months recovery	• Dose-dependent and significant increase of lung wet weight at weeks 1, 7 and 14 post-exposure in the mid- and high-dose groups. • Biochemical parameters in BALF: increase of LDH and β-glu 1 wk after the end of exposure in high-dose group. Increase in both mid- and high-dose groups of protein after 1, 7 and 14 wk, LDH and β-glu after 7 wk post-exposure. • Histopathological findings: all rats (n=5/dose) exhibited dose-dependent very slight to slight accumulation of fibre-laden macrophages, bronchioalveolar hyperplasia, microgranulomas and interstitial fibrosis at wk 14 post-exposure.	Bell-mann 2003

4.7.1.3 Repeated dose toxicity: dermal

No data available.

4.7.1.4 Repeated dose toxicity: other routes

No data available.

4.7.1.5 Human information

No data available.

4.7.1.6 Other relevant information

No data available.

4.7.1.7 Summary and discussion of repeated dose toxicity

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

4.7.1.8 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.

4.7.1.9 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.

4.7.1.10 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.

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

No data available.

4.9 Germ cell mutagenicity (Mutagenicity)

No data available.

4.10 Carcinogenicity

4.10.1 Non-human information

4.10.1.1 Carcinogenicity: oral

No data available.

4.10.1.2 Carcinogenicity: inhalation

	Fibre:	Conc.	Expo.	Duratio	Observations and Remarks	Ref.

Species	**type E**	Total	WHO	L>20 µm	Time (h/day)	n		
AH/HAN rats (n=43)	**104E** **(E)**	-	1022 f/cm^3	≈ 72 f/cm^3	7h/d 5d/wk whole-body	12 months + 12 months recovery or lifetime obs.	• Clearance half-time: 7.1 months • Marked macrophage reaction, thickening of adjacent alveolar walls, and localized but marked fibrosis at the end of the 12-month exposure. Wagner grade = 4. • After 12 additional months of recovery, advanced alveolar fibrosis and bronchoalveolar hyperplasia had developed. • 10/43 rats (23.2%) developed pulmonary tumours (7 carcinomas and 3 adenomas, p=0.02) and 2 had a mesothelioma (4.7%).	Cullen 2000

4.10.1.3 Carcinogenicity: intraperitoneal

Species	Fibre type	Dose			Injection schedule	Duration of observa-tion	Observations and Remarks	Ref.
		Total	WHO	L>20 µm				
Male Wistar rats (n=24)	104E (E)	-	Target: 10^9 f	-	1 x 2 ml saline	lifetime	• Median survival: 642 days. Tumour-associated deaths occurred more quickly than in amosite or 100/475 groups (reported in the Davis 1996 study). • 21/24 rats (88%) treated with 104E had mesothelioma.	Cullen 2000

Female Sprague-Dawley rats	104E (E)	5 mg			1 injection (in 2 ml saline)	lifetime	• Dimensions: median length=4.8 µm and median diameter=0.29 µm • Abdominal tumours were seen in 44/54 (81%) animals • Control (5 mg titanium dioxide): 2/52 (4%) rats had tumours	Pott 1987 Pott 1988
Wistar rats	104E (E)	5 mg			1 injection (in 2 ml saline)	lifetime	• Dimensions: median length=4.8 µm and median diameter=0.29 µm • Abdominal tumours were seen in 20/45 (44%) animals • Control (5 mg titanium dioxide): 0/47 rats had tumours	Pott 1987
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
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	Pott 1976

							mesothelioma, 8 a sarcoma (n=77). Total tumour rate: 71.4% • crocidolite group (2 mg): 15/39 abdominal tumours (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

4.10.1.4 Carcinogenicity: intra-tracheal

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

4.10.1.5 Carcinogenicity: intra-pleural

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

4.10.1.6 Carcinogenicity: dermal

No data.

4.10.2 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, phenolics, silica, styrene and urea. • Special-purpose glass fibres	Marsh 2001 (IARC 2002)

					exposure category: SMR=1.09, 95% CI: 0.87-1.36 (n=81 cases)	

4.10.3 Other relevant information

Test	Fibre type	Cell system	Protocol	Conc. (mg/l)	Observations and Remarks	Ref.
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

4.10.4 Summary and discussion of carcinogenicity

Summary for E-Glass fibres:

Rats were exposed by **inhalation** to **E-glass** in one single study (Cullen *et al*., 2000). E-glass fibres clearly induced marked fibrosis and lung tumours in spite of a short 1-year exposure time and the short size of groups.

By **intraperitoneal** exposure, Cullen *et al*. (2000) showed an increase in the incidence of mesothelioma. Besides, all studies from Pott (1984, 1987 and 1988) clearly report an increased incidence of abdominal tumours following exposure to E-glass fibres by intraperitoneal way. It is observed a dose-response related effect in the studies of Pott 1976 and 1984. It should however be noted that the type of glass (475, E or 753) is not indicated in Pott 1976.

By **intratracheal exposure**, studies were performed with the "JM 104" fibre, corresponding with the both **475 and E-glass fibres**. There is no specific study on the **single E-glass fibre**. In one study (Feron 1985), no lung tumour were found in the hamster but in this study, the crocidolite control-group was also negative. On the other hand, two others studies reported an increase in lung carcinomas in 15% of the animals in rats (Pott 1987) and 27% or 35% of the animals in hamster (Mohr 1984) with an increased incidence with longer fibres.

By **intrapleural route**, there is one study on JM 104 fibres, so it englobes 475, 753 and **E**-glass fibres but it is not specific to **E**-glass fibre (Monchaux 1981). An increase of 13% in mesotheliomas was found in rat with 42% and 54% respectively for chrysotile and crocidolite.

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 (E and 475-glass 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.

4.10.5 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 the E-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 E show a carcinogenic potential by the intraperitoneal route and by inhalation in a well-designed study. Fibre biopersistency may enable their migration further inhalation into the pleural cavity and emphasise the relevance of positive results by the intrapleural route.

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 the 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.

4.10.6 Conclusions on classification and labelling

Overall, largely based on animal evidence, E-glass fibres are presumed to have carcinogenic potential for humans.

However, specifically by inhalation, E-glass fibres clearly induced malign lung tumours so it is specified in the classification of E-glass fibres with "H350i".

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. 1B; H350i is therefore warranted for E-glass fibre (Carc. Cat. 2 – R49 according to the DSD).

4.11 Toxicity for reproduction

No data available.

4.12 Other effects

No data available.

5 ENVIRONMENTAL HAZARD ASSESSMENT

Not relevant for this dossier.

6 OTHER INFORMATION

No other information.

7 REFERENCES

Achard Ellouk S, Jaurand MC. Review of animal / *in vitro* data on biological effects of man-made fibres. Environ Health Perspect 1994; 102 (suppl 2), 47-63

AFSSET, Les fibres minérales artificielles : Evaluation de l'exposition de la population générale et des travailleurs ; « Rapport final relatif aux fibres céramiques réfractaires et aux fibres de verre à usage special »; Saisine n° « 2004-012 » ; janvier 2007.

ATSDR. (2004). Toxicological profile for Synthetic Vitreous Fibres (Atlanta, Georgia, U.S. department of health and human services, Public Health Service, Agency for Toxic Substances and Disease Registry).

Aufderheide M et al. Differences in the biological effects of crocidolite asbestos and two glass fibres on epithelial lung cells. Exp Toxicol Pathol. 1994 Apr;45(8):467-72

Bellmann B, Muhle H, Creutzenberg O et al. Calibration study on subchronic inhalation toxicity of man-made vitreous fibres in rats. Inhalation Toxicology 2003; 15:1147-1177

Blake T et al. Effect of fibre length on glass microfibre cytotoxicity. J Toxicol Environ Health A. 1998 Jun 26;54(4):243-59

Brown DM et al. Effect of coating with lung lining fluid on the ability of fibres to produce a respiratory burst in rat alveolar macrophages. Toxicol in Vitro 1998; 12(1):15-24

Castranova V et al. In vitro effects of large and small glass fibres on rat alveolar macrophages. J Toxicol Environ Health. 1996 Nov;49(4):357-69

Cullen RT et al. Pathogenicity of a special-purpose glass microfibre (E glass) relative to another glass microfibre and amosite asbestos. Inhal Toxicol. 2000 ;12(10):959-77

Cullen RT et al. Short-term inhalation and in vitro tests as predictors of fibre pathogenicity. Environ Health Perspect. 1997 Sep;105 Suppl 5:1235-40

Davis JMG et al. A comparison of methods of determining and predicting the pathogenicity of mineral fibres. Inhalation Toxicology 1996; 8:747-770

Donaldson K et al. Bromo-deoxyuridine (BRDU) uptake in the lungs of rats inhaling amosite asbestos or vitreous fibres at equal airborne fibre concentrations. Exp Toxicol Pathol 1995; 47(2-3):207-11

Eates W et al. Estimating rock and slag wool fibre dissolution rate from composition. InhalationToxicology 2000;12:1127-1139

Feron VJ et al. Pulmonary response of hamsters to fibrous glass: chronic effects of repeated intratracheal instillation with or without benzo[a]pyrene. Carcinogenesis. 1985 Oct;6(10):1495-9

Fisher CE et al. Release of TNF-alpha in response to SiC fibres: differential effects in rodent and human primary macrophages, and in macrophage-like cell lines. Toxicol In Vitro. 2000;14(1):25-31

Fraire AE et al. Effect of fibrous glass on rat pleural mesothelium. Histopathologic observations. Am J Respir Crit Care Med. 1994 Aug;150(2):521-7

Gao HG et al. Morphological transformation induced by glass fibres in BALB-c-3T3 cells. Teratog Carcinog Mutagen 1995; 15(2):63-71

Goldstein et al. Changes produced by the inhalation of glass fibre in non-human primates.). In: Biological effects of a man-made mineral fibres (Proceedings of a WHO/IARC conference), vol. 2, Copenhagen, WHO, 1984, pp 273-285

Hansen K, Mossman BT. Generation of superoxide (O2-.) from alveolar macrophages exposed to asbestiform and nonfibrous particles. Cancer Res. 1987, 15;47(6):1681-6.

Hart GA et al. In vitro cytotoxicity of asbestos and man-made vitreous fibres: roles of fibre length, diameter and composition. Carcinogenesis. 1994 May;15(5):971-7

Hesterberg TW et al. Role of phagocytosis in Syrian hamster cell transformation and cytogenetic effects induced by asbestos and short and long glass fibres. Cancer Res. 1986;46(11):5795-802.

Hesterberg TW et al. Biopersistence of synthetic vitreous fibres and amosite asbestos in the rat lung following inhalation. Toxicol Appl Pharmacol 1998; 151(2):262-75

Hesterberg TW et al. Chronic Inhalation Study of Fibre Glass and Amosite Asbestos in Hamsters: Twelve-month Preliminary Results. Environmental Health Perspectives 1997; 105, Suppl 5; 1223-9

Hesterberg TW, Barrett JC. Dependence of asbestos- and mineral dust-induced transformation of mammalian cells in culture on fibre dimension. Cancer Res. 1984;44(5):2170-80.

IARC. Man-made vitreous fibres. IARC monographs on the evaluation of the carcinogenic risks to humans. Vol 81, 2002. IARC, Lyon, France

INSERM. Effets sur la santé des fibres de substitution à l'amiante. Expertise collective INSERM, Paris, 1999

Jaurand MC. Mechanisms of fibre-induced genotoxicity. Environ Health Perspect 1997; 105 (suppl 5), 1073-84

Johnson NF and Jaramillo RJ. P53, Cip1, and Gadd153 Expression following Treatment of A549 Cells with Natural and Man-made Vitreous Fibres. Environmental Health Perspectives 1997;105, Suppl. 5: 1143-45

Koshi K et al. Cell toxicity, hemolytic action and clastogenic activity of asbestos and its substitutes. Ind Health. 1991;29(2):37-56

Le Bouffant L et al. Experimental study on long-term effects of inhaled MMMF on the lungs of rats. Ann Occup Hyg. 1987;31(4B):765-90

Marchand JL et al. Laryngeal and hypopharyngeal cancer and occupational exposure to asbestos and man-made vitreous fibres: results of a case-control study. Am J Ind Med. 2000 Jun;37(6):581-9

Marsh GM et al. Historical cohort study of US man-made vitreous fibre production workers: I. 1992 fibreglass cohort follow-up: initial findings. J Occup Environ Med. 2001 Sep;43(9):741-56

McConnell EE et al. A comparative study of the fibrogenic and carcinogenic effects of UICC Canadian chrysotile B asbestos and glass microfibre (JM100). In: Biological effects of a man-made mineral fibres (Proceedings of a WHO/IARC conference), vol. 2, Copenhagen, WHO, 1984, pp 234-252

McConnell EE et al. Studies on the inhalation toxicology of two fibreglasses and amosite asbestos in the Syrian golden hamster. Part II. Results of chronic exposure. Inhal Toxicol. 1999 Sep;11(9):785-835

Mikalsen SO et al. Morphological transformation of Syrian hamster embryo cells induced by mineral fibres and the alleged enhancement of benzo[a]pyrene. Carcinogenesis. 1988 Jun;9(6):891-9

Miller BG et al. Influence of fibre length, dissolution and biopersistence on the production of mesothelioma in the rat peritoneal cavity. Ann Occup Hyg. 1999b Apr;43(3):155-66

Miller BG et al. Influence of characteristics of inhaled fibres on development of tumours in the rat lung. Ann Occup Hyg. 1999a Apr;43(3):167-79

Mohr U, Pott F, Vonnahme FJ. Morphological aspects of mesotheliomas after intratracheal instillations of fibrous dusts in Syrian golden hamsters. Exp Pathol. 1984;26(3):179-83

Monchaux G et al. Mesotheliomas in rats following inoculation with acid-leached chrysotile asbestos and other mineral fibres. Carcinogenesis. 1981;2(3):229-36

Moorman WJ et al. Chronic inhalation toxicology of fibrous glass in rats and monkeys. Ann Occup Hyg 1988; 32(suppl1): 757-67

Mossman BT, Sesko AM. In vitro assays to predict the pathogenicity of mineral fibres. Toxicology. 1990 Jan-Feb;60(1-2):53-61

Muhle H et al. Inhalation and injection experiments in rats to test the carcinogenicity of MMMF. Ann Occup Hyg. 1987;31(4B):755-64

Ong T et al. Induction of micronucleated and multinucleated cells by man-made fibres in vitro in mammalian cells. J Toxicol Environ Health. 1997 Mar;50(4):409-14

Pott F, Friedrichs KH, Huth F. [Results of animal experiments concerning the carcinogenic effect of fibrous dusts and their interpretation with regard to the carcinogenesis in humans (author's transl)] Zentralbl Bakteriol [Orig B]. 1976 Aug;162(5-6):467-505

Pott F et al. Animal experiments with chemically treated fibres. Ann Occup Hyg 1988;32:353-359

Pott F et al. New results from implantation experiments with mineral fibres. In: Biological effects of a man-made mineral fibres (Proceedings of a WHO/IARC conference), vol. 2, Copenhagen, WHO, 1984, pp 286-302

Pott F et al. Lung carcinomas and mesotheliomas following intratracheal instillation of glass fibres and asbestos. In: Proceedings of the Vith International Pneumoconiosis Conference, Bochum, Federal Republic of Germany, 20-23 September 1983, vol. 2, Geneva, International Labour Office, 1984, pp. 746-756

Pott F et al. Carcinogenicity studies on fibres, metal compounds, and some other dusts in rats. Exp Pathol. 1987;32(3):129-52

Pott F et al. Animal experiments with chemically treated fibres. Ann Occup Hyg, 1988;32(suppl 1):353-359

Pott F et al. Carcinogenicity studies on natural and man-made fibres with the intraperitoneal test in rats. IARC Sci Publ. 1989;(90):173-9

Pott F et al. Tumours by the intraperitoneal and intrapleural routes and their significance for the classification of mineral fibres. In: Brown RC, Hoskins JA & Johnson NF, eds, Mechanism in Fibre Carcinogenesis (NATO ASI Series 223), New York, Plenum Press, 1991, pp. 547-565

Searl A et al. Biopersistence and durability of nine mineral fibre types in rat lungs over 12 months. Ann Occup Hyg. 1999 Apr;43(3):143-53

Smith DM et al. Long-term health effects in hamsters and rats exposed chronically to man-made vitreous fibres. Ann Occup Hyg. 1987;31(4B):731-54

Wagner JC et al. Animal experiment with MM(V)F – Effects of inhalation and intrapleural inoculation in rats. In: Biological Effects of Man-made Mineral Fibres (Proceedings of a WHO/IARC Conference) vol. 2, Copenhagen, WHO, 1984, pp209-233

Wagner JC et al. Studies of the carcinogenic effects of fibre glass of different diameters following intrapleural inoculation in experimental animals. In: LeVee WN & Schulte PA, eds, Occupational

Exposure to Fibrous Glass (DHEW Publ. No. (NIOSH) 76-151, NTIS Publ. No. PB-258869), Cincinnati, OH, National Institute for Occupational Safety and Health, pp. 193-204

Ye J et al. Critical role of glass fibre length in TNF-alpha production and transcription factor activation in macrophages. Am J Physiol: Lung Cell Mol Physiol 1999; 20(3):L426-34

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.