Committee for Risk Assessment

RAC

Annex 1

Background document

to the Opinion proposing harmonised classification and labelling at Community level of

E-glass microfibres of representative composition

EC number: -
CAS number: -

CLH-O-0000001412-86-34/F

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

04 December 2014

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 fibres of representative composition; [Calcium-aluminium-silicate fibres with random orientation with the following representative composition (% given by weight): SiO2 50.0-56.0%, Al2O3 13.0-16.0%, B2O3 5.8-10.0%, Na2O <0.6%, K2O <0.4%, CaO 15.0-24.0%, MgO <5.5%, Fe2O3 <0.5%, F2 <1.0% with note R. Process: typically produced by flame attenuation and rotary process. (Additional individual elements may be present at low levels; the process list does not preclude innovation).]

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:	E-glass fibres of representative composition; [Calcium-aluminium-silicate fibres with random orientation with the following representative composition (% given by weight): SiO2 50.0-56.0%, Al2O3 13.0-16.0%, B2O3 5.8-10.0%, Na2O <0.6%, K2O <0.4%, CaO 15.0-24.0%, MgO <5.5%, Fe2O3 <0.5%, F2 <1.0% with note R. Process: typically produced by flame attenuation and rotary process. (Additional individual elements may be present at low levels; the process list does not preclude innovation).]
EC number:	-
CAS number:	-
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

[1]Index numbers 650-016-00-2 and 650-017-00-8 in Annex VI of CLP are not applicable

Current entry in Annex VI, CLP Regulation	
Current proposal for consideration by RAC	Carc. 1B – H350i (with note R)
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Carc. 1B – H350i (with note R)

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

1.3 Proposed harmonised classification and labelling based on CLP Regulation

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.

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

In annex VI of Regulation 1272/2008 (CLP), fibres with a harmonised classification are man-made vitreous fibres (MMVF) which are subdivided in two different entries (see table below). The two entries 650-016-00-2 and 650-017-00-8 in CLP refer to "mineral wool" and "refractory ceramic fibres" (RCFs) respectively. These entries are differentiated by name and the chemical composition with respect to the content of alkali/alkali earth metal oxides with 18 % being the cut-off point. Their hazardous properties and harmonised classifications (C&L) also vary from 'suspected carcinogen to humans' (Carc. 2, entry 650-016-00-2) to 'presumed to have carcinogenic potential for humans' (Carc. 1B, entry 650-017-00-8).

Although "special purpose fibres" are explicitly mentioned in the phrasing of the current Refractory Ceramic Fibres entry (index number 650-017-00-8), the appropriate entry for E-glass fibres regarding the alkaline oxide and alkaline earth oxide content (K_{NB} index) should be for "Mineral wool". However, E-glass 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). These discrepancies of the appropriate entry for E-glass fibres requires a new specific entry.

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

In its evaluation, IARC (2002) concluded that there is sufficient evidence in experimental animals for special-purpose glass fibres including E-glass and '475' glass fibres and classified them together as possibly carcinogenic to humans (group 2B). In addition, IARC reported that current average exposure levels to MMVF are generally less than 0.5 respirable fibre/cm^3 (500 000 respirable fibres/m^3) as an 8-h time-weighted average but that higher levels have been measured in production of special-purpose glass fibres, increasing the concern for workers.

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 (Carc. 1B under CLP). However, in October 2006, the

TC C&L agreed to classify 'E-glass fibres' with Carc. Cat. 2; R49 (currently Carc. 1B under CLP) (Follow-up III of TC C&L October 2006; doc ECBI/09/07). Indeed, largely based on animal evidence, E-glass fibres are presumed to have carcinogenic potential for humans. TC C&L discussions (2005, 2006) are added in annex of this dossier. This decision was however not included in an ATP before the entry into force of CLP (2008).

In March 2013, a French proposal for classification was submitted on 'E-glass special purpose fibres' to ECHA followed by a public consultation (PC) from 5 March 2013 until 19 April 2013. During PC, a number of issues were raised by a manufacturer including the incorrect composition and manufacturing process, the confusion in the name between continuous filament glass fibres (not 'respirable') and microfibers ('respirable'). In addition, the manufacturer proposed an alternative name for the substance. In January 2014, the French proposal on 'special purpose E-glass fibres' was withdrawn. The name of the fibres under the CLH proposal has been revised in the present proposal to clarify the scope of the proposal and of the future entry in Annex VI of CLP.

Since TC C&L discussions (2006), there were no new relevant studies of toxicology published on E-fibres with the exception of a review by Bernstein (2007). There is a joint REACH registration dossier on E-glass fibres (E-glass microfibers) which has been taken into account for the completion of this CLH report (registration number 01-2119488048-29-00XX). The registered classification for E-glass microfibres is Carc. 1B – H350i,

In this proposal for harmonised classification, E-glass fibres are proposed to be classified as Carc. 1B – H350i.

Justification for the proposal of a new specific entry:

For the reasons described above, it is therefore proposed to clarify the scope of the original entry to cover E-glass fibres. These fibres are characterized by their chemical composition and physical characteristics (i.e length, diameter and aspect ratio). They are manufactured as continuous filaments, as general purpose insulation fibres with diameters ranging from ca. 5-15 µm and as special purpose fibres of smaller diameters ca. 1-5 microns. It is acknowledged that the meaning of 'special purpose' in this context implies that the fibres are used in applications where a small fibre diameter is required unlike general purpose insulation fibres.

The proposed new entry only refers to E-glass fibres that are respirable. Filaments and non-respirable fibres are not covered by this entry. Note R is therefore included to capture the physical characteristics of the fibres relevant for this classification proposal.

The following naming of the new specific entry is proposed:

'E-glass fibres of representative composition; [Calcium-aluminium-silicate fibres with random orientation with the following representative composition (% given by weight): SiO2 50.0-56.0%, Al2O3 13.0-16.0%, B2O3 5.8-10.0%, Na2O <0.6%, K2O <0.4%, CaO 15.0-24.0%, MgO <5.5%, Fe2O3 <0.5%, F2 <1.0% with note R. Process: typically produced by flame attenuation and rotary process. (Additional individual elements may be present at low levels; the process list does not preclude innovation)].'

Proposal of notes:

The notes A and Q are not proposed for the specific entry of E-glass 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. 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. The note R applies for the fibres with a length weighted geometric mean diameter inferior to 6 µm.

Text of notes (CLP Regulation):

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

In its evaluation, IARC (2002) concluded that there is sufficient evidence in experimental animals for special-purpose glass fibres including E-glass and classified them as possibly carcinogenic to humans (group 2B). In addition, IARC reported that current average exposure levels to MMVF are generally less than 0.5 respirable fibre/cm^3 (500 000 respirable fibres/m^3) as an 8-h time-weighted average but that higher levels have been measured in production of special-purpose glass fibres, increasing the concern for workers.

Respirable fibres are those that can penetrate into the alveolar region of the lung upon inhalation; in humans, a fibre with an aerodynamic diameter of less than 5 µm is respirable according to EPA (2001). Aerodynamic diameter, unlike geometric diameter, takes into account fiber density and aspect ratio (ratio of length to diameter). The World Health Organization (WHO) defines respirable fibres as less than 3 µm in diameter and over 5 µm long, with an aspect ratio of at least 3:1 (WHO 2000).

Nevertheless, carcinogenic differences seem to exist between type ‘475’ and E-glass fibres (Bernstein, 2007). IARC (2002) further reported that the advanced fibrosis induced by E-glass fibres (code 104/E) compared to microfibres (code 100/475) from Cullen *et al*. (2000) were due to the higher number of long fibres of E-glass and their greater biopersistence compared with that of other fibre types.

Indeed, E-glass 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.

The key information used in the REACH registration dossier concluding on Carc. 1B (H350i) is based on Searl *et al*. (1999) and Cullen *et al*. (2000) studies. It is emphasised that 'the studies showed that E-glass microfibre induced fibrosis, carcinomas, adenomas and mesotheliomas in the rat.

Overall, it is concluded that E-glass fibres of representative composition and physical characteristics are presumed to be human carcinogens and should be classified as Carc. 1B (H350) under the CLP Regulation.

2.3 Current harmonised classification and labelling

Not applicable.

2.4 Current self-classification and labelling

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

There is a joint REACH registration dossier on E-glass fibres (E-glass microfibers) which has been taken into account for the completion of this CLH report (registration number 01-2119488048-29-00XX). The registered classification for E-glass microfibres is Carc. 1B – H350i,

For information, other fibres have also been registered using various chemical identifiers as shown in the table below (ECHA dissemination database accessed on 10 February 2014).

Information given in the registration dossier	CAS Number	EC/ListNumber	Proposed C&L	Registration No	Notifications in the C&L inventory
Glass, oxide, chemicals	65997-17-3	266-046-0	Carc. 1B, H350i	01-2119488048-29-XXXX	yes
No name given (Not technically possible following IUPAC rules) *Description: Refractories, alumino-silicate, fibres* Relates to alumino-silicate wools (ASW)	142844-00-6	604-314-4	Carc. 1B, H350	01-2119458050-50-XXXX	Yes (CAS only)
No name given (Not technically possible following IUPAC rules) *Description: Synthetic fibers, alk. earth silicate* Relates to alkaline-earth silicate (AES) fibres	436083-99-7	610-130-5	NC (note Q)	01-2119457644-32-XXXX	Yes (CAS only)

No name given (Not technically possible following IUPAC rules) *Description: Aluminium chloride, basic, reaction products with silica*	675106-31-7	614-074-2	NC	01-2119456884-25-XXXX	No
Man-made vitreous (silicate) fibres with random orientation with alkaline oxide and alkali earth oxide (Na2O+K2O+CaO+ MgO+BaO) content greater than 18 % by weight	-	924-055-3	Carc. 2, H351	01-2119615609-34-XXXX	No
No name given (No IUPAC name allocated) *Description: Man-made vitreous (silicate) fibres with random orientation with alkaline oxide and alkali earth oxide (Na2O+K2O+CaO+MgO+BaO) content greater than 18% by weight and fulfilling one of the note Q conditions* Relates to high alumina, low silica stone wools (HT wools)	-	926-099-9	NC (note Q)	01-2119472313-44-XXXX	No
Amorphous glass product formed from the melting and fiberisation of dipotassium oxide, oxo(oxo-alumanyloxy) alumane and dioxosilane Potassium alumino silicate glass fibre	675106-31-7	931-219-8	NC (note Q)	01-2119962882-26-XXXX	No

NC, not classified

An overview of fibres notified in the C&L inventory (accessed on 10/02/2014) is presented in the table below. For some of these entries, the classification varies from 'not classified' to 'Carc. 1B'. The list number 924-055-3 using the name 'Man-made vitreous (silicate) fibres with random orientation with alkaline oxide and alkali earth oxide (Na2O+K2O+CaO+ MgO+BaO) content greater than 18 % by weight' has not been used by notifiers.

Index Number	EC/list Number	CAS Number	Name	Overview of Notifications of classification according to CLP
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 (Na2O+K2O+CaO+MgO+BaO) content greater than 18 % by weight]	None [CLP: Carc. 2 (H351) (with notes R, Q and A)]
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 (Na2O+K2O+CaO+ MgO+BaO) content less or equal to 18 % by weight]	None [CLP: Carc. 1B (H350i) (with notes R and A)]
-	-	142844-00-6	Aluminosilicate (ceramic) fiber Aluminosilicate refractory ceramic fibres Refractories, fibers, aluminosilicate not technically possible following IUPAC rules	Carc. 1B (H350) with or without notes (70 notifications)

-	-	436083-99-7	Alkaline Earth Silicate Fibres	NC or Carc. 2 (H351) with or without notes (25 notifications)
-	-	-	Man-made vitreous (silicate) fibres with random orientation with alkaline oxide and alkali earth oxide (Na2O+K2O+CaO+ MgO+BaO) content greater than 18 % by weight Man-made vitreous (silicate) fibres with random orientation with alkaline oxide and alkali earth oxide (Na2O+K2O+CaO+ MgO+BaO) content greater than 18 % by weight	Carc. 2 (H351) with or without notes (2 notifications)
-	-	-	Man-made vitreous (silicate) fibres with random orientation with alkaline oxide and alkali earth oxide (Na2O+K2O+CaO+MgO+BaO) content greater than 18 % by weight No IUPAC name assigned	Carc. 2 (H351) with or without notes (11 notifications)
-	-	-	Man-made vitreous (silicate) fibres with random orientation with alkaline oxide and alkali earth oxide (Na2O+K2O+CaO+ MgO+BaO) Reaction mass of aluminium oxide and silicon dioxide	NC or Carc. 1B (H350) with or without notes (5 notifications)
-	-	-	Aluminosilicate Refractory Ceramic Fibres	Carc. 1B (H350) with notes R & A (2 notifications)
-	-	-	Zirconia Aluminosilicate Refractory Ceramic Fibres	Carc. 1B (H350) with notes R & A (1 notification)
-	266-046-0	65997-17-3	glass, oxide, chemicals (other names include fiberglass),	NC to Carc. 1B (H350) with no note (> 500 notifications)

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 fibres of representative composition and physical characteristics have CMR properties, i.e. carcinogenic property, that justifies a harmonised classification and labelling according to article 36 of CLP.

Considering the recommendations of IARC (2002), TC C&L (2006) and the REACH registration dossier (registration number 01-2119615609-34-XXXX), harmonisation of classification is considered to be required for this endpoint (carcinogenicity) .

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 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. The physical characteristics (length, diameter, aspect ratio) determine the applications in which they are used. The proposed entry is specific to those E-glass fibres that are respirable. Continuous filaments and non-respirable fibres are outside the scope of the entry.

Table 4: Substance identity

EC number:	-
EC name:	-
CAS number (EC inventory):	-
CAS number:	-
CAS name:	-
Name(s) in the IUPAC nomenclature or other international chemical name(s)	E-glass special purpose fibres of representative composition; [Calcium-aluminium-silicate fibres with random orientation with the following representative composition (% given by weight): SiO2 50.0-56.0%, Al2O3 13.0-16.0%, B2O3 5.8-10.0%, Na2O <0.6%, K2O <0.4%, CaO 15.0-24.0%, MgO <5.5%, Fe2O3 <0.5%, F2 <1.0% with note R. Process: typically produced by flame attenuation and rotary process. (Additional individual elements may be present at low levels; the process list does not preclude innovation).]
CLP Annex VI Index number:	Not applicable
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 5: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
E-glass fibres	Ca 100%	-	-

Table 6: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
None	-	-	-

Table 7: 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 8: 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		

RAC general comment

In annex VI of Regulation 1272/2008 (CLP), fibres with a harmonised classification are man-made vitreous fibres (MMVF) which are subdivided into two different entries (see table below).

Index No	International Chemical Identification	Hazard Class and Category Code(s)	Hazard statement Code(s)	Notes
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

The two existing entries in the CLP Regulation with index numbers 650-016-00-2 and 650-017-00-8 cover '*mineral wool*' and '*Refractory Ceramic Fibres, Special Purpose Fibres*', respectively. These entries are differentiated by name and the chemical composition with respect to the content of alkaline oxides and alkali earth metal oxides with 18 % by weight being the cut-off point. Their hazardous properties and harmonised classifications (CLH) are 'suspected human carcinogens' (Carc. 2) and 'presumed human carcinogens' (Carc. 1B), respectively.

The CLH proposal originally submitted by the Dossier Submitter (DS) refers to glass fibres within the glass wool category and therefore continuous filaments are not within scope of the proposal. In addition, a new entry in Annex VI needs to be created for the E-glass microfibres of representative composition. This class of glass wool fibres consists of fine glass fibres forming a mass resembling wool; individual fibres are defined as being over 5 µm long and having a length-to-width (aspect) ratio of at least 3:1 (i.e., the fibre is at least three times as long as its width). There is considerable variation in the physico-chemical properties of individual fibres within this class, depending on the manufacturing process and end use. It is well-known that relatively small changes in composition can result in significant changes in the optical and electrical properties of the glass fibres. For example C-glass fibres are resistant to chemical attack, S-glass fibres have a high strength whereas E-glass fibres are poor conductors of electricity. A specific glass wool product often contains fibres with a wide range of diameters, as a result of the manufacturing process.

The manufacturing process also determines the particle length and diameter of the fibres. The methods of manufacture determine whether a fibre is a "General Purpose Fibre" or a "Special Purpose Fibre". "Special Purpose Fibres" are characterised by having a diameter

< 5µm while "General Purpose Fibres" are having a diameter > 5µm. A fibre of a given chemical composition can be either a "Special Purpose Fibre" or a "General Purpose Fibre" depending on the method of manufacture (E-glass fibres for example can be either general purpose insulation fibres or special purpose fibres). Special purpose fibres are referred to in this report as "microfibres" as this terminology is used in industry and is more representative than "special purpose". The typical process to produce the E-glass microfibres of representative composition is by flame attenuation and rotary process.

For cancer hazard identification, it is important that fibres are classified according to their biological activity, including their biopersistence *in vivo* (Bernstein, 2007). The E-glass microfibres considered in this document are characterised with respect to the contents of alkaline oxides and alkali earth metal oxides ($Na_2O+K_2O+CaO+MgO+BaO$) being greater than the current 18% by weight cut-off as described in existing Annex VI entries for fibres. E-glass microfibres have a lower alkaline oxides and alkali earth metal oxides content than glass fibres of representative composition and also a higher content of Al_2O_3 (Campopiano *et al*., 2014).

Recognising the range of biological effects induced by various types of glass fibres, France submitted a proposal for harmonised classification of E-glass microfibers. During the first public consultation (PC) of the CLH report (5 March to 19 April 2013), a number of issues were raised by manufacturers and downstream users including the incorrect composition and manufacturing process details, the confusion in the name between continuous filament glass fibres ("not respirable") and microfibres ("respirable "). In addition, manufacturers and downstream users proposed an alternative name for the substance. In November 2013, the French proposal was withdrawn for further consideration and in February 2014, a new dossier was submitted to ECHA by France on "E-glass fibres of representative composition" followed by a new PC from 5 March 2014 until 22 April 2014. After PC, the DS agreed to rename the "fibres" as "microfibres" to distinguish between respirable "E-glass microfibres" and "E-glass Continuous Filament Glass Fibres" which are not respirable.

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 is not necessary.

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 harmonised 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)	MMVF32(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	Hesterberg 1998 (Eastes 2000)
	MMVF33 (475)	36±8 mg/m^3	371±55 f/cm^3	163±25 f/cm^3			<u>475-glass:</u> • 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 harmonised 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 harmonised 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 harmonised 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 harmonised 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

Species	**Fibre: type E**	Conc.			Expo. Time (h/day)	Duration	Observations and Remarks	Ref.
		Total	WHO	L>20 µm				
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 mesothelioma, 8 a sarcoma (n=77).	Pott 1976

							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.	Mon-chaux 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.	Mar-chand 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.	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	Marsh 2001 (IARC 2002)

			Control: US or local county mortality rates		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 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, 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.

The reach registration dossiers do not reported additional key studies.

Classification by IARC in 2002:

In its evaluation, IARC (2002) concluded that there is sufficient evidence in experimental animals for special-purpose glass fibres (E-glass) and classified them as possibly carcinogenic to humans (group 2B), as for refractory ceramic fibres.

Human data:

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 CLP 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 (respirable) 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.

E-glass fibres are characterized by their chemical composition and physical characteristics (i.e length, diameter and aspect ratio). They are manufactured as continuous filaments, as general purpose insulation fibres with diameters ranging from ca. 5-15 µm and as special purpose fibres of smaller diameters ca. 1-5 microns. It is acknowledged that the meaning of 'special purpose' in this context implies that the fibres are used in applications where a small fibre diameter is required unlike general purpose insulation fibres.

The proposed new entry only refers to E-glass fibres that are respirable. Filaments and non-respirable fibres are not covered by this entry. Note R is therefore included to capture the physical characteristics of the fibres relevant for this classification proposal. Respirable fibers are those that can penetrate into the alveolar region of the lung upon inhalation; in humans, a fibre with an aerodynamic diameter of less than 5 µm is respirable according to EPA (2001). Aerodynamic diameter, unlike geometric diameter, takes into account fiber density and aspect ratio (ratio of length to diameter). The World Health Organization (WHO) defines respirable fibres as less than 3 µm in diameter and over 5 µm long, with an aspect ratio of at least 3:1 (WHO 2000).

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. E-glass fibres clearly induced malign lung tumours after inhalation.

A classification as Carc. 1B; H350i is therefore warranted for respirable E-glass fibres of representative composition (Carc. Cat. 2 – R49 according to the DSD) with the addition of Note R.

RAC evaluation of carcinogenicity

Summary of the Dossier submitter's proposal

E-glass microfibres of representative composition [Calcium-aluminium-silicate fibres with random orientation with the following representative 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%] are proposed to be classified as Carc. 1B – H350i. The DS further proposed adding Note R, which, according to Annex VI of the CLP Regulation, states that the classification as a carcinogen needs not apply to fibres with a length weighted geometric mean diameter less two standard geometric errors greater than 6 µm.

The DS presented the available toxicology studies by different routes of exposure (inhalation, intraperitoneal, intratracheal, intrapleural) as well as a summary of the available human information. The DS concluded that the potential for carcinogenic effects is confirmed by inhalation in a well-designed study with E-glass microfibres. E-glass microfibres induce a marked macrophage reaction, alveolar fibrosis and hyperplasia which may indicate a progressive pathway to neoplastic transformation of respiratory cells, whereas glass microfibres of representative composition (analogous to commercial grade or type '475' glass microfibres and special purpose glass fibres with comparable chemical compositions of 'Evanite B' and 'Laucher B-glass') do not exhibit such effects by inhalation (Cullen, 2000). Besides, a comparison between the carcinogenic potential by the intraperitoneal route (Pott, 1984) shows that 32% of rats had abdominal tumours with E-glass microfibres, although only 4% of rats had abdominal tumours with type '475'-glass fibres.

Overall, the DS has concluded that E-glass microfibres of representative composition are presumed to be human carcinogens and should be classified as Carc. 1B – H350i under the CLP Regulation with note R assigned to the entry in Annex VI to the CLP Regulation.

Comments received during public consultation

No comments were submitted objecting to the proposed classification. Two MSCAs supported the classification, but suggested some editorial improvements and one MSCA requested additional substantiation of the proposed classification in order to fulfil the CLP requirement to demonstrate carcinogenicity of the E-glass microfibres in more than one species. Five industrial organisations indicated a need to rename the substances from "fibres" to "microfibres" which was supported by the DS and also taken into account in this opinion. The CLH report will however not be updated but additional information will be available in Annex 2 to the opinion (Response to comments document, RCOM).

Assessment and comparison with the classification criteria

Summary of animal studies

Inhalation studies:

In the study of Cullen *et al*. (2000) the carcinogenic potency of E-glass fibres 104E, glass microfibres analogous to type '475' and amosite asbestos were compared after chronic inhalation exposure and after intraperitoneal injection in rats. Rats were exposed for 12 months to aerosol concentrations of 1000 fibres (longer than 5 µm)/mL, as measured by optical microscopy, for 7 h/day, 5 days/week. Subgroups of rats were examined for mean

lung burden, early and late signs of fibrosis, and tumour incidence.

From the inhalation study using a subgroup of 43 animals exposed to E-glass (104E) microfibres, 10 (23%) rats had lung tumours (7 carcinomas, 3 adenomas) and 2 (5%) had mesotheliomas, whereas in 42 rats exposed to amosite asbestos, there were 16 (38%) lung tumours (7 carcinomas, 9 adenomas) and 2 (5%) mesotheliomas.

The E-glass fibres (104E) and amosite-treated animals had similar levels of fibrosis. In contrast, 38 (88%) rats treated with glass microfibres (100/475) had little fibrosis, 4 (10%) had lung tumours (adenomas), and no animal had mesotheliomas.

The study provided evidence for carcinogenicity of E-glass microfibres by the inhalation route of exposure.

The greater pathology induced by the E-glass microfibres, referred to as commercial type grade or type 104E, compared to the other glass microfibres (commercial grade or type 100/475 microfibres), might be partly explained by the greater numbers of long fibres retained in the lung after 12 months of inhalation. However, it is possible that modification of surface properties by extensive selective leaching of some glass components reduces the toxic potential of the commercial grade or type 100/475 microfibres.

At the end of 12 months of exposure, the mean number of grade or type 104E fibres of all lengths in the lungs was approximately double that for amosite, but two-thirds of that for 100/475 microfibres. For fibres longer than 15 µm, the mean grade or type 104E burden was similar to that for the amosite and more than twice that of the 100/475. After a 12-month recovery period, the retained lung burdens (of fibres of all lengths) were approximately 30% of those at 12 month for both microfibres, and somewhat higher (approximately 44%) for amosite. Amosite and 100/475 fibres longer than 15 µm were more persistent in the lungs than grade or type 104E fibres.

The chemical composition of grade or type 104E fibres did not appear to have been significantly altered by up to 24 months of residence in lung tissue, whereas the composition of type 100/475 was substantially altered over the same time period.

In a parallel intraperitoneal injection study, grade or type 104E caused considerably more mesotheliomas (21 rats out of 24) than 100/475 (8 rats out of 24). In addition, grade or type 104E appeared to be more active than amosite asbestos, since mesotheliomas appeared much more quickly in the grade or type 104E-treated animals. The results of this study demonstrated that two microfibre types, 100/475 and 104E, of similar dissolution rates, had markedly different potency in rats. In the opinion of the authors (Cullen *et al*., 2000), this contrast is only partly due to differences in numbers of long fibres and the differences in surface properties of the fibres, possibly due to proportionately greater leaching of 100/475 fibres, play an important role.

Intratracheal studies:

Two intratracheal instillation studies in hamsters were reported by the DS in the CLH report, but the exact type and composition of glass microfibres used (types '475', 'E' or '753') was not indicated by the authors (Feron *et al*., 1985; Mohr *et al*., 1984) suggesting that these fibres were administered together. An overview of the study results after intratracheal instillation is provided in the Table below.

Tumour incidences (%) in animals after intratracheal instillation of glass microfibres in rats and hamsters (in bold; where applicable, negative control was TiO_2; positive control was crocidolite asbestos)		
Reference and species	Type of microfibres used in the study	Number and percentage of Tumours (lung tumours and mesotheliomas)

Pott, 1987 (rat)	'475' crocidolite	**5/34 (15%)** (1 adenoma, 4 carcinomas) 15/35 (43%)
Smith, 1987 (rat)	'475' crocidolite	**0%** 8%
Feron, 1985 (hamster)	'475', '753' and/or E glass fibres (mixture or chemical composition unknown)	**0** **(0%)**
Mohr, 1984 (hamster)	'475', '753' and/or E glass fibres (two lengths, mixture or chemical composition unknown) crocidolite TiO_2	**48/136 (35%)** (with median fibres length of 7µm) **38/138 (27%)** (with median fibres length of 4.2 µm) 18/42 (13%) 2/135 (1.5%)

In the absence of identification of the specific type of glass fibres and information on their composition in some of the studies, it is concluded that results of these studies using intratracheal instillation do not allow a conclusion to be drawn on their carcinogenic potential by this route of exposure.

Intraperitoneal injection studies:

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

Intrapleural injection studies

There is no adequate study by this route for E-glass microfibres. According to the CLH report, there is a study on 'JM 104' type fibres (Monchaux *et al*., 1981 reported by IARC, 2002) conducted by the intrapleural route with uncertain significance for the assessment of the carcinogenicity of E-glass microfibres.

According to the CLH report, there is a study on 'JM 104' type fibres (Monchaux *et al*., 1981 reported by IARC, 2002) conducted by the intrapleural route with uncertain significance for the assessment of the carcinogenicity of E-glass microfibres. In that study, groups of 32–45 male SPF Sprague-Dawley rats, three months of age, received single intrapleural injections of 20 mg of 'JM 104' (types 475, 753 or E) (chemical composition not given) (mean length, 5.89 µm; mean diameter, 0.229 µm) (chemical composition not given), 20 mg UICC chrysotile A (mean dimensions, 3.21 µm × 0.063 µm) or 20 mg UICC crocidolite (mean dimensions, 3.14 µm × 0.148 µm) in 2 mL saline, or received 2 mL saline alone. Animals were kept until natural death; the mean survival times for whole groups (and for animals with tumours) were 513 (499), 388 (383), 452 (470) and 469 days, respectively. An overview of the study results after intrapleural injection is provided in the Table below (from IARC, 2002).

Tumour incidences (%) in animals after intrapleural injection of glass fibres in rats (in bold; where applicable, positive controls are indicated)			
Reference and species	Type of microfibres used in the study	Mean survival time in days (time for animals with tumours)	Number and percentage of Tumours (mesotheliomas only)
Monchaux *et*	None (saline)	469 (-)	0/32 (0)

al., 1981 (SD rats)	'475', '753' and/or E glass fibres (mixture or chemical composition unknown) chrysotile crocidolite	513 (499) 388 (383) 452 (470)	**6/45 (13%)** 15/33 (45%)* 21/39 (54%)

* including one rat with a carcinoma; -, no animals with tumours

RAC concludes that 'JM 104' type of glass microfibres are capable of inducing mesothelioma in rats after intrapleural injection, but the carcinogenic potency is less than that of chrysotile or crocidolite. However, in the absence of identification and composition of the microfibres administered, it is not possible to conclude whether this study provides evidence for carcinogenicity of E-glass microfibres.

Summary of human studies

A case-control study did not show any association between laryngeal or hypopharyngeal cancers and microfibre exposure (Marchand *et al*., 2000) but the study included a very small number of microfibre-exposed subjects. In an historical cohort study (Marsh *et al*., 2001), an excess of respiratory cancer was observed in the general glass-fibre group of workers 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.

Comparison with the classification criteria

According to criteria in Annex 1 of the CLP Regulation (Table 3.6.1), in order to classify a substance in Category 1B for carcinogenicity (i.e. presumed to have carcinogenic potential for humans), classification should be largely based on evidence derived from animal experiments which is sufficient to demonstrate animal carcinogenicity (presumed human carcinogen). It is further clarified in the CLP Regulation, Annex 1, Section 3.6.2.2.3.(b) "Carcinogenicity in experimental animals" that it is possible to conclude:

"*sufficient evidence of carcinogenicity if :*

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."

Glass microfibres are poorly soluble minerals which only undergo selective leaching and dissolution. Major determinants of toxicity are the form and size of the fibres, surface chemistry, and bio-persistence. Crystal structure, chemical composition, origin, and associated minerals, as well as trace contaminants, all modulate surface chemistry; and transformation, translocation, and solubility of the fibres in body fluids influence their biopersistence, a factor which modulates cumulative exposure (IARC, 2012). In relation to fibre dimension and deposition, one can assume that there exists a continuum of the carcinogenic potency of respirable fibres, which increases with length. Biopersistence of a fibre increases tissue burden, and therefore, may increase any toxicity the fibre might possess. For synthetic vitreous fibres, there is evidence from studies in animals that the potential for carcinogenicity increases with biopersistence (IARC, 2012; WHO, 2005). RAC recognised that glass microfibres which have the relevant dimensions and which are bio-persistent should be considered *de facto* carcinogenic.

RAC also recognizes that inhalation, is the major route of exposure in humans and therefore relevant for classification. Oral and dermal exposure routes are not considered relevant for glass microfibres. However, other non-physiological routes (e.g. intraperitoneal) and exposure regimens (e.g. single intratracheal administration) are considered relevant for hazard assessment. These non-physiological routes usually increase the sensitivity to a toxic response, mimicking worst-case exposure and biopersistence. According to WHO (2005), carcinogenicity testing of fibres by intraperitoneal injection represents a sensitive assay compared with rat inhalation studies.

The experimental data clearly provided evidence of a carcinogenic effect of E-glass microfibres by inhalation exposure in rats (Cullen *et al*. 2000). By intraperitoneal exposure, Cullen *et al*. (2000) showed an increase in the incidence of mesothelioma in rats. Besides, other studies from Pott (1984, 1987 and 1988) clearly report an increased incidence of abdominal tumours following intraperitoneal exposure to E-glass microfibres. This experimental data fulfils the criterion of sufficient evidence of carcinogenicity, since the carcinogenic effects were observed in two or more independent studies in one species carried out at different times or in different laboratories, or under different protocols.

Therefore RAC agrees with the proposal from the DS that E-glass microfibres warrant classification as Carc. 1B with hazard statement H350i: "May cause cancer by inhalation".

RAC also agrees with the proposed route-specific classification for inhalation (H350i). It is highly improbable that exposure by the dermal or even oral route would lead to a carcinogenic response, taking into account that long-term deposition of the E-glass microfibres in the tissues, as can occur in lung, is a prerequisite for carcinogenicity.

Comparison with criteria for applying notes specific to fibres

Note A, Q and R are specific to fibres and cover different aspects that condition their classification and labelling in Annex VI of CLP. The two existing entries in the CLP Regulation with index numbers 650-016-00-2 and 650-017-00-8 contain notes A, Q, R and A, R (respectively) which are described in Annex VI of the CLP regulation.

The two existing entries in the CLP Regulation with index numbers 650-016-00-2 and 650-017-00-8 also contain notes A, Q, R and A, R (respectively) which are described as follows in Annex VI to the CLP Regulation:

Note 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 of Annex VI. 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.

Note Q :

The classification as a carcinogen need not 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.

Note R :

The classification as a carcinogen need not apply to fibres with a length weighted geometric mean diameter less two standard geometric errors greater than 6 µm.

The applicability or not of these notes is also part of the RAC opinion on E-glass microfibers and discussed further below.

For E-glass microfibres, RAC proposes to apply **note A** from Annex VI of the CLP Regulation, which states that 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. Table 3.1: List of harmonised classification and labelling of hazardous substances.

RAC is of the opinion that E-glass microfibres should **not** be marked with **note R** from Annex VI of the CLP Regulation, which states that "*classification as a carcinogen need not apply to fibres with a length weighted aerodynamic geometric mean diameter less two standard geometric errors (LWGMD) greater than 6 µm*". The test method was published in Commission Regulation (EC) No 761/2009 (EC, 2009). The measurement method for the LWGMD under note R was created to characterise the fibre diameter of bulk substances or products containing man-made mineral fibres (MMMF, including Refractory Ceramic Fibres, man-made vitreous fibres (MMVF), crystalline and polycrystalline fibres. The length weighting is a means of compensating for the effect on the diameter distribution caused by the breakage of long fibres when sampling or handling the material. Geometric statistics (geometric mean) are used to describe the size distribution of MMMF diameters, because their diameters usually approximate to log normal distributions (ECB, draft 4). RAC concluded that note R is a measure for diameter and not length. The methods of manufacture given in the name of the entry (rotary and flame attenuation) and the name itself 'microfibres' also discount continuous filaments and also would not generate fibres with diameters > 6 µm. Indeed, the typical methods of manufacturing processes reported in publicly available literature (i.e. mostly from industry) are flame attenuation and rotary process, which determine the diameter of the fibre. The ranges of nominal diameters produced for these microfibres are less than 3 microns for rotary blowing process and less than 2-4 microns for flame attenuation process. This means that the LWGMD is not applicable to E-glass microfibres.

RAC is also of the opinion that E-glass microfibres of representative composition should not be marked with **note Q**. Indeed, the experimental evidence shows biopersistence and excessive carcinogenicity which does not allow an exemption of the classification as a carcinogen.

Finally, with regards to the identity of the substance, it is stated that "additional individual elements may be present at low levels". These elements, although at low levels and dependent on the manufacturing process, may influence both the toxicity and the biopersistence of the glass microfibres. It is also stated in the substance identity that "the

process list does not preclude innovation" because there may be other "fiberisation" technologies or methods not covered in the proposed naming (e.g. Fi-high speed F-Technology).

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.

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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.