Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

Glass microfibres of representative composition

EC number: -
CAS number: -

CLH-O-0000001412-86-35/F

Adopted

04 December 2014

04 December 2015

CLH-O-0000001412-86-35/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonized classification and labelling (CLH) of:

Chemicals name: glass microfibres of representative composition
EC number: -

CAS number: -

The proposal was submitted by **France** and received by RAC on **14 February 2014.**

In this opinion, all classifications are given in the form of CLP hazard classes and/or categories.

PROCESS FOR ADOPTION OF THE OPINION

France has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation*** on **5 March 2014**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **22 April 2014.**

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by RAC: **Bogusław Barański**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation. The comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonized classification and labelling was reached on **4 December 2014**.

The RAC Opinion was adopted by **consensus**.

OPINION OF THE RAC

RAC adopted the opinion that **glass microfibers of representative composition** should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal	TBD	Glass microfibres of representative composition; Calcium-aluminium-silicate fibres with random orientation with the following composition (% given by weight): SiO_2 55.0-60.0%, Al_2O_3 4.0-7.0%, B_2O_3 8.0-11.0%, ZrO_2 0.0-4.0%, Na_2O 9.5-13.5%, K_2O 0.0-4.0%, CaO 1.0-5.0%, MgO 0.0-2.0%, Fe_2O_3 <0.2%, ZnO 2.0-5.0%, BaO 3.0-6.0%, F_2 <1.0%. 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).]	-	-	Carc. 2	H351	GHS08 Wng	H351			R
RAC opinion	TBD				Carc. 2	H351 (inhalation)	GHS08 Wng	H351 (inhalation)			A
Resulting Annex VI entry if agreed by COM	TBD				Carc. 2	H351 (inhalation)	GHS08 Wng	H351 (inhalation)			A

SCIENTIFIC GROUNDS FOR THE OPINION

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)	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

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) also vary from 'suspected human carcinogens' (Carc. 2) to '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 these 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 glass microfibres of representative composition is by flame attenuation and rotary process.

It is noted that a specific glass composition manufactured to have typically a diameter < 3 µm is known in the industry literature as grade or type '475'. Type '475' is a commercial name from one manufacturer and there are many commercial fibres that have the same composition and characteristics (diameter/length). As it was one of the most commonly tested glass fibre types, many literature reports refer to type '475' and 'special purpose' glass fibres. According to Bernstein (2007), type '475' microfibres are produced in many different diameters based on customer needs, but the most commonly sold products have mean diameters between 0.65 µm and 2.7 µm. According to Bernstein (2007), comparable microfibres other than grade or type '475' includes those with trade names 'Evanite B' and 'Laucher B-glass'.

For cancer hazard identification, it is important that fibres are classified according to their biological activity, including their biopersistence *in vivo* (Bernstein, 2007). The glass microfibres considered in this document with respect to the contents of alkaline oxides and alkali earth metal oxides as described in Annex VI of CLP (Na_2O +K_2O+CaO+MgO+BaO) being 13.5 – 30.5% by weight, have a mean content which is spread over the current 18% cut-off as described in existing Annex VI entries for fibres. Glass microfibres have a higher alkaline oxides and alkali earth metal oxides content than E-glass fibres of representative composition and also a lower content of Al_2O_3 (Campopiano *et al*., 2014).

Recognising the differentiation of biological effects of various types of glass fibres France submitted a proposal for the harmonised classification of 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 (M/DU) including the incorrect composition and manufacturing process details. In addition, '475' was considered as a proprietary name to a M/DU. In November 2013, the French proposal was withdrawn. In February 2014, a new CLH dossier was submitted to ECHA on 'glass fibres of representative composition with SiO_2 55.0-60.0%, Al_2O_3 4.0-7.0%, B_2O_3 8.0-11.0%, ZrO_2 0.0-4.0%, Na_2O 9.5-13.5%, K_2O 0.0-4.0%, CaO 1.0-5.0%, MgO 0.0-2.0%, Fe_2O_3 <0.2%, ZnO 2.0-5.0%, BaO 3.0-6.0%, F_2 <1.0%' followed by a PC from 5 March to 22 April 2014. After PC, the DS agreed to rename 'fibres' as 'microfibres' to distinguish between respirable 'glass microfibres' and 'glass Continuous Filament Glass Fibres' which are not respirable.

RAC evaluation of carcinogenicity

Summary of the Dossier submitter's proposal

Glass microfibres of representative composition [Calcium-aluminium-silicate fibres with random orientation with the following composition (% given by weight): SiO2 55.0-60.0%, Al2O3 4.0-7.0%, B2O3 8.0-11.0%, ZrO2 0.0-4.0%, Na2O 9.5-13.5%, K2O 0.0-4.0%, CaO 1.0-5.0%, MgO 0.0-2.0%, Fe2O3 <0.2%, ZnO 2.0-5.0%, BaO 3.0-6.0%, F2 <1.0%] were proposed by the DS to be classified as Carc. 2; H351. 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 studies by different routes of exposure (inhalation, intraperitoneal, intratracheal, intrapleural) as well as a summary of the available human information. The DS concluded that no study clearly demonstrated the induction of tumours following inhalation of glass microfibres of representative composition (microfibres analogous to commercial grade or type '475'). However most of the available studies have considerable limitations.

Overall, the DS concluded that glass microfibres of representative composition are suspected to be human carcinogens and should be classified as Carc. 2 (H351) under the CLP Regulation with note R assigned to the new entry in Annex VI of CLP.

Comments received during public consultation

No comments were submitted objecting to the proposed classification. Two MSCAs supported classification but suggested some editorial improvements. One industrial organisation 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. One industrial organisation pointed out two references already included in the CLH report which provided data supporting different classifications for E-glass microfibres and glass microfibres. The CLH report will however not be updated but additional information is 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 none of the several inhalation toxicity studies on rats exposed for 12-30 months to glass microfibres (microfibres analogous to commercial grade or type '475') was any significant increase in lung tumour or lung fibrosis frequency observed (Davis, 1996; Miller, 1999a; Cullen, 1997; Le Bouffant *et al.*, 1984; Le Bouffant *et al*., 1987; Hesterberg, 1997; Muhle, 1987; McConnel, 1984, 1999; Moorman, 1988; Smith, 1987; Wagner, 1984).

However, as the DS pointed out, several important limitations were identified in these studies such as insufficient exposure duration (Muhle *et al*., 1987, Moorman *et al*., 1988), use of short fibres as test materials (Le Bouffant, 1984, Muhle *et al*., 1987, Smith *et al*., 1987), no data on fibre dimensions (McConnell *et al*., 1984), no (asbestos) positive control group (Le Bouffant *et al.* 1987, Moorman *et al*., 1988) and no data on animal survival (Le Bouffant, 1984 Wagner *et al*., 1984). The absence of a significant induction of tumours with asbestos in Muhle *et al*. (1987) and Smith *et al*. (1987) raises questions concerning the relevance of these studies in the present evaluation.

The detailed review (Bernstein, 2007) of the available toxicology data on glass microfibres (such as type '475' special-purpose glass fibres) clearly showed that following inhalation of these fibres even at relatively high doses, the glass microfibres '475' were not fibrogenic and did not cause tumours. The available data clearly showed pathological differences between the glass microfibres analogous to grade or type '475' and the E-glass microfibres and support treating these two types of fibres independently.

The greater pathology induced by the E-glass microfibres, referred to as commercial type grade or type '104E', compared to 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' fibres. 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 '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 microfiber types, '100/475' and '104 E', 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 that differences in surface properties of the fibres, possibly due to proportionately greater leaching of '100/475' fibres, play an important role.

In hamster studies, Smith *et al*. (1987) observed no tumours in animals exposed to microfibres analogous to type '475' glass (2.4 mg/m^3, 3000 f/cm^3, median dimensions: 4.7 µm in length (mean 7.5 µm) and 0.45 µm in diameter (mean 0.4 µm), 6h/d, 5d/week) or crocidolite for 24 months.

In the study by McConnell *et al*. (1999) with exposure to 37 mg/m^3 microfibres analogous to type '475' for 78 weeks (310 f/cm^3; 109 f/cm^3 with L > 20 µm, 6h/d, 5d/week), 1 hamster (2%) had a mesothelioma. It was accompanied by pleural fibrosis and mesothelial hyperplasia in 22% of the animals.

Two inhalation studies were performed on monkeys exposed to microfibres analogous to type '100/475'. The monkeys were sacrificed at the end of the exposure (Moorman *et al*., 1988; Goldstein *et al*., 1984). No tumours were reported in cynomolgus monkeys after 18 months of exposure to 5 mg/m^3 (dimensions: diameter < 3.5 µm; group 3: length > 10 µm and group 4: length < 10 µm, 7h/d, 5d/week) (Moorman *et al*., 1988) or in baboons after 30 months of exposure to 1000 f/cm^3 (Goldstein *et al*., 1984). Longer exposures and observation periods would have been required to detect neoplasms in such animals. Peribronchiolar fibrosis was observed in the study from Goldstein *et al*. (1984).

Overall it is concluded that there is not sufficient evidence of carcinogenicity of glass microfibres of representative composition (microfibres analogous to type '475') in inhalation studies on animals.

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). They are inconclusive for the hazard assessment of E-glass microfibres. Further details are given in the BD.

Intraperitoneal injection studies:

Several studies are available on rats (mainly Wistar) by the intraperitoneal (IP) route for '475' glass microfibres and E-glass microfibres. In all studies, the animals received a single IP injection ranging from 2 to 25 mg '475' glass fibres or mixture of '475', 'E' and '753' glass fibres. The animals were kept for lifetime observation (limited to 130 weeks in the study from Pott, 1989). It should also be noted that the the mixture of '475', 'E' and '753' was applied in studies of Pott et al. (1976) and Pott (1984).
In Pott et al. (1976), the median fibre length was either 10 µm or 3 µm and the median diameter was 0.2 µm or 0.4 µm, respectively, in the two parts of the study.
In Pott et al. (1984) the dimensions of '475' glass fibres were: median length = 10 µm and median diameter = 0.2 µm.
In Pott (1987, high dose) the median length of the '475' glass fibres were 2.4 µm and the median diameter was 0.33 µm.
In Pott et al. (1987, low dose) the median length of the '475' glass fibres were 3.2 µm and the median diameter was 0.18 µm.

In Pott et al. (1989) the median length of the '475' glass fibres was 2.6 µm and the median diameter was 0.15 µm.
In Davis et al. (1996) the mean diameter of the '475' glass fibres were 0.32 µm.
In Smith et al. (1987) the dimensions of the '475' glass fibres were: median length: 4.7 µm and median diameter 0.4 µm.

In the study of Pott (1984), E-glass microfibres at doses of 2 and 20 mg caused abdominal tumours in 32% of rats (14/44) and in 66% of rats (29/44), respectively. Chrysotile induced abdominal tumours in 20% of rats (9/44), 59% of rats (26/44) and in 79% of rats (35/44) at doses of 0.4, 2 and 10 mg, respectively. Type '475' glass microfibres induced abdominal tumours in 4 % of rats (2/44).

An increased incidence of abdominal mesotheliomas (4%) and sarcomas (64%) was observed in rats dosed intraperitoneally with 2 mg, 10 mg or 4x25 mg of '475' glass microfibres (Pott *et al*., 1984, 1987, 1989, 1991, Davis *et al*., 1996, Miller *et al*., 1999b, Smith *et al*., 1987). The frequency of abdominal tumours in saline-treated control rats were in the range of 0-6%. When two dose levels were used, a positive trend between tumour incidence and dose was observed (Pott *et al*., 1976, 1984 and 1987).

It is concluded by RAC that the results of the studies demonstrate carcinogenicity of glass microfibres after intraperitoneal application, although carcinogenic potential of glass microfibres of representative composition analogous to type '475' by this route is significantly less than that of E-glass microfibres and asbestos (chrysotile, crocidolite).

Intrapleural injection studies:

Four groups of 25 BALB/c mice (sex and age unspecified) received single intrapleural injections of a high dose of 10 mg of one of four different samples of borosilicate glass fibres (chemical composition not given) in 0.5 mL distilled water. The material for injection was obtained by separating each of two original samples with average diameters of 0.05 µm and 3.5 µm into two samples, one with lengths of several hundred microns and the other with lengths of < 20 µm. Animals were killed at intervals of two weeks until 18 months of exposure (a total of 37 mice survived at this time). No pleural tumour was found in any of the treated animals, whereas mesotheliomas were observed in 2/150 mice given intrapleural injections of chrysotile or crocidolite (dose not stated) in a parallel experiment. The IARC Working Group noted the small number of animals used, the relatively short observation time and the low response in the positive controls (Davis, 1976 quoted from IARC (2002)).

Groups of 32–36 SPF Wistar rats (twice as many males as females), 13 weeks of age, received single intrapleural injections in 0.4 mL saline of 20 mg glass fibre (a borosilicate; 30% of fibres 1.5–2.5 µm in diameter; maximum diameter, 7 µm; 60% > 20 µm in length) (chemical composition not given), 20 mg glass powder (a borosilicate; diameter < 8 µm) or 20 mg of one of two different samples of Canadian SFA chrysotile. Rats were kept until natural death; the average survival times were 774, 751, 568 and 639 days for the groups treated with glass fibres, glass powder and the two chrysotile samples, respectively. No injection-site tumour was observed in the group treated with glass fibres; a single mesothelioma occurred in the group treated with glass powder (after 516 days). The incidences of tumours in the two groups treated with chrysotile were 23/36 and 21/32; the first deaths of animals with tumours occurred after 325 and 382 days (Wagner *et al*., 1973 quoted from IARC, 2002).

Three groups of 16 male and 16 female Wistar rats, 10 weeks of age, received single intrapleural injections of 20 mg of fine US 'JM 100' glass fibres (type '475', 99% of fibres < 0.5 µm in diameter; median diameter, 0.12 µm; 2% > 20 µm in length; median length, 1.7 µm) (chemical composition not given) or a coarser "US" 'JM 110' glass fibres (type '475', 17% of fibres < 1 µm in diameter; median diameter, 1.8 µm; 10% > 50 µm in length; median length, 22 µm) (chemical composition not given) in 0.4 mL saline or saline alone.

Animals were kept until natural death; mean survival times were 716, 718 and 697 days for the mice treated with fine fibres, coarse fibres and saline, respectively. Between 663 and 744 days

after inoculation, 4/32 animals given the finer glass fibres had mesotheliomas. No pleural tumours occurred in animals treated with the coarser glass fibres or in controls that received saline (Wagner *et al*., 1976 quoted from IARC, 2002).

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 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' type of glass fibres (consisting of types 475, 753, E) (chemical composition not given) (mean length, 5.89 µm; mean diameter, 0.229 µm), 20 mg UICC chrysotile A (mean dimensions, 3.21 µm x 063 µm), 20 mg UICC crocidolite (mean dimensions, 3.14 µm x 0.148 µm) in 2 ml saline or 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. The incidences of thoracic tumours were as follows: the group that received glass fibres, 6/45 (mesotheliomas); groups treated with chrysotile and crocidolite, 15/33 (1 carcinoma and 14 mesotheliomas) and 21/39 (mesotheliomas), respectively. No thoracic tumours occurred in the 32 control animals (Monchaux *et al*., 1981 quoted from IARC, 2002).

Following intrapleural injection of glass fibres of type '475' (20 mg, single dose), mesotheliomas were consistently reported in 8 to 12% of the animals in three different rat studies (Wagner *et al*., 1984, Fraire *et al*., 1994, Wagner *et al*., 1976). In Fraire *et al*. (1994), fibrosis was also observed in 75% of animals and mesothelial hyperplasia in 66%.

An overview of the study results after intrapleural injection is provided in the Table below (from IARC, 2002).

Tumour incidences (%) and other respiratory lesions in rats after intrapleural injection of glass fibres of type '475'

Reference	Type of microfibres used in the study	Fibres length & diamater	Mesothelioma (neg. controls/pos. controls)	Chronic inflammation (and fibrosis)	Mesothelial dysplasia	Hyperplasia
Monchaux *et al*., (1981)	'475', 753 and/or E	Mean fibre length=5.89 µm and mean diameter =0.229 µm	13 (0/42-54)	-	-	-
Wagner (1984)	'475'	88% <5 µm in length and 98.5 < 1 µm in diameter	8 (0/12)	-	-	-
Fraire (1994)	'475'	Mean length=2.2 µm and mean diameter= 0.15 µm	12.5	37.5 (75)	37.5	66.6
Wagner (1976)	'475'	mean fibre length=1.7 µm and mean diameter= 0.12 µm	12.5 (4/32) vs. 0 in neg. controls (0/32)	-	-	-

It is concluded by RAC that the results of the studies demonstrate the carcinogenicity of glass microfibres after intrapleural application, although carcinogenic potency of glass microfibers of

representative composition by this route is much less than that of E-glass microfibres and asbestos (chrysotile, crocidolite).

Summary of human studies

In a case-control study conducted by Marchand *et al*. (2000), 315 incident cases of laryngeal cancer, 206 cases of hypopharyngeal cancer, and 305 hospital-based controls with other types of cancer were recruited in 15 hospitals in six French cities. The subjects' past occupational exposure to asbestos and to four types of MMVF (mineral wool, refractory ceramic fibres, glass filaments, and microfibres) was evaluated based on their job history, with the aid of a job-exposure matrix. The authors concluded that asbestos and mineral wools (may) have a carcinogenic effect on the epilarynx and the hypopharynx. Due too few subjects exposed to these microfibers, the authors were unable to draw conclusions on their carcinogenicity.

In a historical cohort study (Marsh *et al*., 2001), a 6 % excess of respiratory system cancer compared to local rates (16 % compared to national rates) was observed in the general glass fibre group but not in the special–purpose glass fibres sub-group. The size of this sub-group was also limited (n=81).

Overall, as proposed by the DS, RAC concludes that these data are not considered sufficient to draw any conclusion on the potential carcinogenic effects in humans.

Comparison with the classification criteria

RAC recognised that glass microfibres which have the relevant dimensions and which are bio-persistent should be considered *de facto* carcinogenic. They 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 bio-persistence, a factor which modulates cumulative exposure (IARC, 2012). In relation to fibre dimension and deposition, one can assume that there exists a continuum variation on the carcinogenic potency of respirable fibres, which increases with length. Bio-persistence of a fibre increases tissue burden, and therefore, may increase any toxicity the fiber might possess. For synthetic vitreous fibres, there is evidence from studies in animals that the potential for carcinogenicity increases with bio-persistence (IARC, 2012; WHO, 2005).

RAC also recognises that the relevant route of exposure for classification is inhalation which is also the major route of exposure in humans. 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 bio-persistence. According to WHO (2005), carcinogenicity testing of fibres by intraperitoneal injection represents a sensitive assay compared with rat inhalation studies.

According to criteria of Annex 1 of the CLP Regulation (Table 3.6.1), in order to classify a substance in Category 2 for carcinogenicity i.e. suspected to have carcinogenic potential for humans, classification should be largely based on animal evidence derived from animal experiments for which there is evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B, based on strength of evidence together with additional considerations (see section 3.6.2.2 of CLP). Such evidence may be derived either from limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.

Taking into account the lack of carcinogenicity of glass microfibres of representative composition in several inhalation studies in rats, hamsters and monkeys, a very weak carcinogenic potential in intratracheal studies, some carcinogenic potential by intraperitoneal and intrapleural injections,

RAC is of the opinion that glass microfibres of indicated representative composition warrant classification as Carc. 2. It is however recognised that most of the studies have methodological limitations. Therefore RAC agrees with the proposal from the DS that glass microfibres of representative composition warrant classification as Carc. 2 with hazard statement H350: "May cause cancer". The route of exposure inhalation shall also be added after the hazard statement code.

Comparison with criteria for applying notes specific to fibres

The two existing entries in the CLP Regulation with index numbers 650-016-00-2 and 650-017-00-8 contained also 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.

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 the glass microfibres of representative composition 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 MMMFs 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 glass microfibres.

RAC is also of the opinion that 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).

Additional references not included in the CLH report

EC (2009) Commission Regulation (EC) No 761/2009 of 23 July 2009 amending, for the purpose of its adaptation to technical progress, Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (Text with EEA relevance).

ECB (draft 4 under revision). ECB/TM/1(00) rev.2. Length weighted aerodynamic geometric mean diameter of fibres. Accessed on 09/02/2015 at http://tsar.jrc.ec.europa.eu/documents/Testing-Methods/DRAFTlwgmd-4.pdf

Le Bouffant L, Henin JP, Martin JC, Normand C, Tichoux G & Trolard F. (1984) Distribution of inhaled MMMF in the rat lung—Long-term effects. In: *Biological Effects of Man-Made Mineral Fibres* (Proceedings of a WHO/IARC Conference), Vol. 2, Copenhagen, World Health Organization, pp. 143–167

Le Bouffant L, Daniel H, Henin J, Marti, JC, Normand C, Thichoux G and Trolard F. (1987) Experimental study on long-term effects of inhaled MMMF on the lungs of rats. Ann. occup. Hyg. 31, 765–790.

Oberdörster G. (2002). Toxicokinetics and effects of fibrous and nonfibrous particles. Inhalation Tox. 14:29–56.

Campopiano, A, Cannizzaroa, A, Angelosantoa, F, Astolfib ML, Ramiresa D, Oloria A, Caneparib S, Iavicolia S. (2014). Dissolution of glass wool, rock wool and alkaline earth silicate wool: Morphological and chemical changes in fibres. Regul. Toxicol. Pharmacol. 70(1): 393-406.

HSE Health and Safety Laboratory, An inventory of fibres to classify their potential hazard and risk. Health and Safety Executive 2006

ANNEXES:

Annex 1 Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in RAC boxes.

Annex 2 Comments received on the CLH report and response to comments provided by the Dossier Submitter and by RAC (excl. confidential information).