# Committee for Risk Assessment

# RAC

Annex 2

**Response to comments document (RCOM)**

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

**E-glass microfibres of representative composition**

**EC number: -**

**CAS number: -**

CLH-O-0000001412-86-34/F

**Adopted**

**4 December 2014**

**COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON E-GLASS FIBRES OF REPRESENTATIVE COMPOSITION**

**COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION**

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.
All attachments including confidential documents received during the public consultation have been provided in full to the dossier submitter, to RAC members and to the Commission (after adoption of the RAC opinion). Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website.

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**Substance name: E-glass microfibres of representative composition**
**CAS number: -**
**EC number: -**
**Dossier submitter: France**

## GENERAL COMMENTS

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 18.04.2014 | Belgium | European Owens Corning Fiberglas SPRL | Company-Manufacturer | 1 |

Comment received

Our comments are related to the substance name [E-glass fibres of representative composition], not to the proposed classification. Our comments were partly considered at the previous consultation.
However there are changes due in order to clearly define the scope and intent of this entry and thus avoid misunderstanding by users of "E-glass fibres". Indeed E-glass is the composition of 'E-glass Continuous Filament Glass Fibres' as well as 'E-glass microfibres'.
Therefore it is proposed to have the following name adopted:
Substance name: E-glass microfibres 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).]
Justification for change of substance name:
• "E-glass fibres" term is usually associated with Continuous Filament Glass Fibre ("CFGF") products which are used as plastic reinforcement in the composite material supply chain.
• Indeed, E-glass is the common glass composition for CFGF products. E-glass Continuous filaments fibres annual worldwide production is ca. 3 million tons whereas E-glass microfibers are produced in the magnitude of one hundred tons per year.
• The on-going CLH report consultation is already triggering inquiries by CFGF users and customers, indicating that the proposed substance name is misleading. Even downstream trade associations that know our CFGF products for many years are mislead by the substance name and have expressed concerns regarding the classification of our products.
• As emphasised in the CLH report, the substance name needs to reflect the physical characteristics (length, diameter and aspect ratio) because this is the primary criteria for fibre hazard classification. Indeed the vast majority of E-glass fibre are not carcinogenic

since not respirable. Therefore 'microfibre' in the substance name is needed to designate adequately and clearly which E-glass fibres category is covered by the hazard classification.
• The "Note R" included in the full description is not sufficient to bring clarity and understanding in the supply chain.
• The proposed change is consistent with the actual wording used in the CLH report to distinguish between 'E-glass microfibre' and 'E-glass Continuous Filament Glass Fibre'. Therefore it is only consistent to change the substance name accordingly.
Conclusion
We strongly advise to replace the name 'E-glass fibres' by 'E-glass microfibres' to ensure consistency between the substance name and the actual intend of the current CLH report and proposed hazard classification. This change will better serve the purpose of the CLH dossier and avoid unfounded and detrimental concerns related E-glass Continuous Filaments Glass Fibre products.

Dossier Submitter's Response

We appreciate the concerns that E-glass is widely used as both filaments, fibers and microfibers. Filaments are not covered by the current proposal as clearly indicated with both the method of manufacture (flame attenuation) and note R. However, because the proposed entry in Annex VI of CLP Regulation is specific for microfibers, for clarity in terms of scope, we agree that it is to be included in the name.

The revised name would then be: E-glass microfibres 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).]

RAC's response

RAC has adopted this proposal for rephrasing the name of the substance as:
E-glass microfibres 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).]

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 18.04.2014 | Netherlands | PPG Industries Fiber Glass EMEA | Company-Manufacturer | 2 |

Comment received

These comments are related to the substance name, but NOT to the proposed classification. Our comments were partly considered at the previous consultation.
However there are changes due in order to clearly define the scope of this entry and thus avoid misunderstanding by users of "E-glass fibre" because E-glass is the composition of 'E-glass Continuous Filament Glass Fibre' as well as 'E-glass micro fibre' (see attached file).

Dossier Submitter's Response

See response to comment 1.

RAC's response

See response to comment 1.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 10.04.2014 | France | Saint-Gobain ADFORS | Company-Importer | 3 |

Comment received

These comments are related to the substance name, but NOT to the proposed classification. Our comments were partly considered at the previous consultation.
However there are changes due in order to clearly define the scope of this entry and thus avoid misunderstanding by users of "E-glass fibre" because E-glass is the composition of 'E-glass Continuous Filament Glass Fibre' as well as 'E-glass micro fibre.
Therefore it is proposed to have the following name adopted:
Substance name: E-glass microfibres 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).]
The change of substance name is needed because:
- E-glass fibre is usually associated with CFGF - Continuous Filament Glass Fibre - for the reason that CFGF production ranges in the magnitude of several million tons per years, whereas E-glass microfibre is produced in the magnitude of 100 tons per year.
- The on-going CLH report consultation triggered inquiries by CFGF users already, indicating that the proposed substance name is misleading. Even downstream trade associations that know our CFGF product for many years were misled by the substance name and expressed concerns regarding the classification of our product.
- As emphasised in the CLH report, the substance name need to reflect the physical characteristics (length, diameter and aspect ratio) because this is the primary criteria for fibre hazard classification. Indeed the vast majority of E-glass fibre are not carcinogenic since not respirable. Therefore 'microfibre' in the substance name is needed to indicate physical characteristics.
- The proposed change is consistent with the actual wording used in the CLH report to distinguish between 'E-glass Continuous Filament Glass Fibre' and 'E-glass microfibre'. Therefore it is only consistent to change the substance name accordingly.

Therefore we strongly advise to replace the name 'E-glass fibre' by 'E-glass microfiber' to ensure consistency between the substance name and the actual intend of the current CLH report.

Dossier Submitter's Response

See response to comment 1.

RAC's response

RAC has adopted this proposal for rephrasing the name of the substance as:
E-glass microfibres 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).]

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 14.04.2014 | Sweden | | MemberState | 4 |

| Comment received |
|---|
| The Swedish CA supports classification of 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).] (CAS No. not assigned) as specified in the proposal. SE agrees with the rationale for classification into the proposed hazard class and differentiation.<br><br>We assume that the date of the CLH report indicated on the front page should be February 2014. |
| Dossier Submitter's Response |
| Thank you for your support. |
| RAC's response |
| RAC takes a note of the Swedish CA support for the classification proposed by DS |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 11.04.2014 | Germany | P-D Glasseiden GmbH Oschatz | Company-Manufacturer | 5 |
| Comment received | | | | |
| 'These comments are related to the substance name, but NOT to the proposed classification. Our comments were partly considered at the previous consultation. However there are changes due in order to clearly define the scope of this entry and thus avoid misunderstanding by users of "E-glass fibre" because E-glass is the composition of 'E-glass Continuous Filament Glass Fibre' as well as 'E-glass micro fibre' (see attached file). | | | | |
| Dossier Submitter's Response | | | | |
| See response to comment 1. | | | | |
| RAC's response | | | | |
| See response to comment 1. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 16.04.2014 | Germany | | MemberState | 6 |
| Comment received | | | | |
| DE CA supports the French proposal to classify 'E-glass fibres of representative composition' as possibly carcinogenic to humans. The proposal of assignment of the note R is also supported. However some misrepresentations and inconsistencies in the French CLH report should be corrected. | | | | |
| Dossier Submitter's Response | | | | |
| Thank you for your support. | | | | |
| RAC's response | | | | |
| RAC takes note of the German CA support for the classification proposed by DS | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 16.04.2014 | Germany | Johns Manville Europe GmbH | Company-Manufacturer | 7 |

| Comment received |
|---|
| In 2013 we submitted comments related to the name of the substance. Although some of our comments have been considered and the name of the substance adapted, there is still a lot of potential for confusion. Therefore we suggest renaming the substance as follows: E-glass **microfibres** 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).<br>We only ask to add the word "microfibre" to the name in order to avoid any confusion with the Continuous Filament Glass Fibres, which are not respirable and therefore not covered by this dossier.<br>We support the request of our Association GlassFibreEurope and add their comment with the rationale as an attachment. Also we attach our comments from April 2013 which contains a detailed rationale for our request. |
| Dossier Submitter's Response |
| See reponse to comment 1. |
| RAC's response |
| See response to comment 1. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 25.03.2014 | Belgium | GlassFibreEurope | Industry or trade association | 8 |
| Comment received | | | | |
| These comments are related to the substance name, but not to the proposed classification. Our comments were partly considered at the last consultation.<br>However there are changes due in order to clearly define the scope of this entry and thus avoid misunderstanding by users of "E-glass fibre" because E-glass is the composition of 'E-glass Continuous Filament Glass Fibre' as well as 'E-glass micro fibre' (see attached file). | | | | |
| Dossier Submitter's Response | | | | |
| See reponse to comment 1. | | | | |
| RAC's response | | | | |
| See response to comment 1. | | | | |

**CARCINOGENICITY**

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 14.04.2014 | Sweden | | MemberState | 9 |
| Comment received | | | | |
| The Swedish CA agrees that there is sufficient evidence from studies in several species of animals for concluding that E-glass fibres of representative composition (CAS No. not assigned) induce benign and malignant lung tumours and abdominal tumours by different routes of exposure (inhalation, intraperitoneal, intratracheal and intrapleural). Furthermore, in animals exposed to E-glass fibres by inhalation, effects which may indicate a progressive pathway to neoplastic transformation of respiratory cells (marked macrophage reaction, alveolar fibrosis and hyperplasia) were observed. A study in rats showed that the frequency of animals with abdominal tumours following intraperitoneal exposure to E-glass fibres and type "475" glass fibres was 32% and 4%, respectively, suggesting that the carcinogenic | | | | |

potential of two types of fibres is different. The available data warrants classification in Carc. 1B; H350i.

The Swedish CA agrees that a new specific entry is required for E-glass fibres (of special-purpose type), since, in Annex VI of CLP, the entry for fibres with a harmonised classification is man-made vitreous fibres (MMVF) subdivided into the two different entries with index number 650-016-00-2 and 650-017-00-8, referring to mineral wool (classification Carc. 2; H351) and refractory ceramic fibres/special purpose fibres (classification Carc. 1B; H350i), respectively. Neither of these entries is appropriate for E-glass fibres; with respect to "special purpose fibres", the entry for E-glass fibres would be refractory ceramic fibres with the classification Carc. 1B; H350i and, with respect to the content of alkaline oxide and alkaline earth oxide specified for the two entries, the entry for E-glass fibres would be mineral wool with the classification Carc.2; H351. Accordingly, a new specific entry is required for E-glass fibres (of special-purpose type). The proposed classification for E-glass fibres is Carc. 1B; H350i.

The Swedish CA agrees with the naming and notes of the proposed new specific entry for E-glass fibres.

| Dossier Submitter's Response |
|---|
| Thank you for your comment and for your support. |
| RAC's response |
| RAC agrees with the Swedish CA proposals on classification and requirement of a new specific entry for E-glass fibres (microfibres) of indicated representative composition |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 16.04.2014 | Germany | | MemberState | 10 |
| Comment received | | | | |
| 'E-glass fibres of representative composition' show a carcinogenic potential in rats exposed by inhalation and by intra-peritoneal injection. Marked fibrosis and lung tumours were observed in rats after repeated exposure by inhalation for one year. Rats received a single intra-peritoneal injection of 'E-glass fibres of representative composition' developed an increased incidence of mesothelioma.<br>The available epidemiological data do not demonstrate sufficient evidence of carcinogenicity in human. In comparison to the given criteria for the CLP Regulation these 'E-glass fibres of representative composition' fulfil the criteria for a category 1B carcinogen with the hazard statement H350.<br><br>However the proposed route-specific classification for inhalation (H350i) needs a prominent statement. According to the CLP criteria a route could only be stated if proven that no other route of exposure exhibits the hazard.<br>Further the following misrepresentations and inconsistencies in the CLH report should be corrected:<br>In section 2.2, p11 it is noted that the key information for the proposal to classify 'E-glass fibres of representative composition' as Carc. 1B (H350i) is based on Searl et al. (1999) and Cullen et al. (2000) studies. However information from the Searl et al. (1999) study is not described in the CLH report.<br>In section 4.10.5, p28 it is noted that experimental data for the 'E-glass fibres of representative composition' have shown a clear carcinogenic effect in several species (rats, hamsters and monkeys). But data from monkeys are not described in the CLH report. | | | | |

| Dossier Submitter's Response |
|---|
| Thank you for your comment.<br>According to the CLP criteria (p 399), the intra-peritoneal route is considered as being a non-physiological route of exposure. Indeed, it is an unexpected route of exposure for human in the real life. Besides, France considers that the main physiological route of human exposure to these fibres is by inhalation. Other routes of exposure (oral or dermal) are not expected. Hence, France thinks that the specification of the route of exposure by inhalation "H350i" for the characterisation of the carcinogenicity hazard is appropriate.<br><br>Thanks for the careful proof reading. The study from Searl et al. 1999 is specific from "glass of representative composition fibres" (former "475" fibres) and not specific to 'E-glass fibres of representative composition'. It should be deleted from this specific CLH report for 'E-glass fibres of representative composition'. The purpose of this study was to provide comparable estimates of the biopersistence of a range of fibre types, for the study of general relationships with other biological and toxicological responses.<br><br>The study presenting effects in monkeys is the study of Moorman et al., 1988 "Chronic inhalation toxicology of fibrous glass in rats and monkeys". Here is the abstract of this study:<br>"A long term inhalation study was conducted with 500 F344 rats and 60 Cynomolgus monkeys in 5 treatments, in 4 of which they were exposed to aerosolized glass fibres of varying geometry and mass. Exposures of 5 or 15 mg/m$^3$ with long or short lengths, with and without binder were provided for 18 months to monkeys and for 21 months to rats which were subsequently held to 80% mortality. Biological responses evaluated include life table analysis, body weights, clinical signs, haematological testing, respiratory function, ophthalmological examinations, clinical biochemical analysis, and gross and microscopic pathological examinations. Both species demonstrated pulmonary macrophage aggregates and granulomata containing fibrous glass. Rats had grossly visible pleural plaques which were not seen in the monkeys. Fibrogenicity or carcinogenic responses were not seen except for a significantly increased incidence of mononuclear cell leukaemia in each fibre-exposed rat group." |
| RAC's response |
| Thank you for editorial comments and support for the proposed classification.<br>RAC agrees that the reference Searl *et al*. (1999) should not have been included in the CLH report in the key information. Some other information e.g. in section 4.10.5, p28 regarding results in monkeys have been considered differently in the opinion.<br><br>Concerning the proposed route-specific classification for inhalation (H350i), RAC agrees with the proposal by DS. It is highly unprobable that exposure by the dermal or even the oral route would lead to a carcinogenic response taking into account that long-term deposition of the E-glass microfibres in the tissues as occurred in lung is a prerequisite for carcinogenicity. It does not seem appropriate to request long term carcinogenicity studies by the oral or dermal route to prove that no other route of exposure exhibits the hazard as required by the CLP criteria, knowing that inhalation is the dominant route, if not the only route, through which man can be exposed in occupational and environmental scenarios. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 22.04.2014 | Belgium | | MemberState | 11 |
| Comment received | | | | |

We acknowledge that E-glass fibres cause tumours in rats as observed in Cullen study.

In order to support the classification, we would recommend the DS to substantiate its proposal by detailing the findings/the studies.

According to the guidance, Carcinogen category 1B where classification is largely based on animal evidence … defined as 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 (sufficient evidence)

The DS is proposing Carc. Cat 1B H350i ; May cause cancer by inhalation. This classification is based only on one study in one species. The DS is advised to complete its proposal in order to fulfill the criteria for Cat. 1B.

For example, the Cullen (2000) study indicates marked macrophage reaction, thickening of adjacent alveolar walls and localized but market fibrosis at the end of the 12-month exposure. However, there is no information on the number of animals presenting those effects nor if these are the same animals presenting the pulmonary tumours after the 12 months of recovery.

We recommend the DS to consider the repeated dose toxicity studies via inhalation route and specially to complete the data (number of animals affected) For example, Bellemann study (2003) indicates histological findings in a dose dependent manner (however no information on the animals) like bronchioalveolar hyperplasia which can contribute to the Weight of Evidence for carcinogenic potential.

We notice on page 28 that the DS refers to carcinogenic effects observed in monkeys however there is no study on monkeys in the proposal.

Dossier Submitter's Response

Thank you for your comment. The data requested are provided below while available.

This classification is based on more than two different species (a):

-Male Wistar rats (Cullen et al 2000), female Sprague-Dawley rats (Pott et al., 1987, and 1988), Wistar rats (Pott et al., 1987), female Wistar rats (Pott 1984, Pott 1976),
-Male Syrian golden hamster (Mohr, 1984),
-Monkeys (Moorman et al., 1988)

The study presenting effects in monkeys is the study of Moorman et al., 1988 "Chronic inhalation toxicology of fibrous glass in rats and monkeys". (unfortunately the description of this study is missing in the CLH report): it is the study for which few details are available. Here is the abstract of this study:
"A long term inhalation study was conducted with 500 F344 rats and 60 Cynomolgus monkeys in 5 treatments, in 4 of which they were exposed to aerosolized glass fibres of varying geometry and mass. Exposures of 5 or 15 mg/$m^3$ with long or short lengths, with and without binder were provided for 18 months to monkeys and for 21 months to rats which were subsequently held to 80% mortality. Biological responses evaluated include life table analysis, body weights, clinical signs, haematological testing, respiratory function, ophthalmological examinations, clinical biochemical analysis, and gross and microscopic pathological examinations. Both species demonstrated pulmonary macrophage aggregates

and granulomata containing fibrous glass. Rats had grossly visible pleural plaques which were not seen in the monkeys. Fibrogenicity or carcinogenic responses were not seen except for a significantly increased incidence of mononuclear cell leukaemia in each fibre-exposed rat group."

And this classification proposal is based on (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols (sufficient evidence):
-Cullen 2000, Pott 1976, Pott 1984, Pott 1987, Pott 1988, Monchaux 1981 in rats.

Here are some precisions on the Cullen study (2000):

**Design of the study:**
This article (Cullen et al, 2000) describes the activity of an E-glass microfiber (104E) during chronic inhalation and intraperitoneal injection studies in rats. Results are compared with another microfiber, the microfiber with the code 100/475 and the more durable amosite asbestos.

**Design of the chronic inhalation study (12 months of exposure):**
83 male Wistar (AF/HAN) strain rats were exposed (whole body) to aerosol concentrations of 1000 fibers/ml (longer than 5 µm), as measured by optical microscopy, for 7h/day, 5 days/week, for up to 12 months. They were allowed to recover for up to a further 12 months. The lung burdens of groups of 6 animals were measured after 6, 9, and 12 months of exposure and following the end of 12 months exposure, after recovery periods up to 12 months. For each time points during exposure, rats were left for 3 days before sacrifice to allow clearance of fibers from the main conducting airways. 47 rats that had been exposed for 12 months were assigned for pathological investigations, with 4 rats being sacrificed at the end of of 12 months inhalation for evaluation of early fibrosis, and 43 retained to follow the production of tumors and long-term fibrosis. During the course of these experiments, a control group of 38 animals was maintained in conventional grid-bottomed cages for their natural life span in order to provide information on spontaneous pulmonary tumor development and fibrosis.

**Design of histopathology analysis:**
At the end of the 12 months inhalation period, 4 rats out of the 47 allocated for pathology were sacrificed to examine levels of tissue damage and fibrosis. The remaining 43 rats were allowed to live out their full life span, to allow tumor development, until only 6 survived, at which point this part of the study was terminated. All lungs were examined histologically for the presence of neoplasms. The estimates of advanced alveolar interstitial fibrosis in the oldest animals were made for the last 9 dying within 2 months of the final sacrifice date.

**Results of histopathology analysis:**
At the completion of the 12 months of inhalation exposure to E microfibers, **4 rats** out of the 47 allocated for pathology were sacrificed to provide lungs for histological evaluation of the development of fibrosis. The rat lungs already showed considerable pathological changes, most of them centered around the terminal bronchioles and respiratory bronchioles. In these areas, for the 4 rats examined, there was a marked macrophage reaction and the walls of adjacent alveoli were thickened, mainly by the rounding of alveolar epithelial cells, but also with the production of some new connective-tissue fibers. Fibrosis was particularly marked at the bifurcations of the small airways themselves, where small nodular lesions had developed. These lesions were classified as Wagner Grade 4, but showed little extension to include the surrounding alveoli. Two of the animals showed single small patches where alveolar wall fibrosis had spread away from the terminal bronchioles.

0.3% of the lung parenchyma was estimated as the area of these small lesions within the 4 animals sacrified at 12-mo (data not shown). Comparison with animals which were sacrified later in the study indicated that the fibrosis became progressively more widespread with time.
By 2 years (12 mo inhalation + 12 mo of recovery), significant areas of advanced alveolar fibrosis and bronchoalveolar hyperplasia (BAH) had developed, and in those 9 animals that survived until the termination of the study, the mean area of these lesions was 8.0% of lung parenchyma (table 5).

TABLE 5. Lung fibrosis 12 mo after the end inhalation: Minimum, maximum, and mean level of advanced fibrosis (% of lung area)

| Fiber type | Animals for fibrosis (number) | Level of advanced fibrosis (% of lung area) | | |
|---|---|---|---|---|
| | | Minimum | Mean | Maximum |
| 104E | 9 | 1.1 | 8.0 | 12.5 |
| 100/475 | 11 | 0.0 | 0.2 | 0.7 |
| Amosite | 9 | 3.5 | 7.6 | 14.8 |
| Controls | 15 | 0.0 | 0.08 | 0.6 |

This value was similar to that for amosite asbestos but much higher than for glass microfiber code 100/475. Occasional areas of fibrosis/BAH do occur in old control animals, but the mean area of fibrosis for 15 control animals was only 0.08%.

**Tumor development:**
Numbers of rats **(from the same group of the 4 rats killed for histopathology analysis)** developing pulmonary tumors after inhalation exposure: among the 43 long-term survivors exposed to 104E fibers, **7 rats** had **carcinomas** and **3** had **benign adenomas**. Two of 38 control rats of similar ages to the treated rats developed pulmonary tumors, 1 adenoma and 1 carcinoma. There was a statistically significant higher tumor (adenoma + carcinoma) incidence rate among rats exposed to 104E compared to control rats ($p$ = 0.026). Although tumor incidence among 104E-exposed rats was higher than for 100/475-exposed rats and lower than for amosite, neither of these differences was statistically significant using Fisher's exact test (both $p > .10$).

However, for the 104E fibers group, the incidence of carcinomas specifically was comparable with amosite asbestos and significantly higher than for the 100/475 fibers group ($p$ = 0.02). The number of adenomas for amosite (9) was higher than for 104E (3) or 100/475 (4) or controls (1). Mesotheliomas were produced only among rats exposed to 104E and amosite, although in both cases the numbers were low and the incidence was similar (about 5%). One of the two 104E rats with mesotheliomas also had a carcinoma.

In the **Bellmann study (2003)**,
-the number of animals for toxicity investigations are represented in the table below:

## Toxicity Investigations

The endpoints and the number of animals assigned to these investigations are listed in Table 4.

**TABLE 4.** Investigations during the study

| Investigation | Test required after start of exposure (mo) | Number of animals for single investigation |
|---|---|---|
| Lung retention of test material | 3; 4.5; 6 | 5 |
| Bronchoalveolar lavage | 3; 4.5; 6 | 5[a] |
| Histology/proliferation test (BrdU) | 3; 4.5; 6 | 5 |

*Note.* Exposure was terminated after 3 mo; subgroups were kept for further 3 mo for recovery investigations.

[a]Eight animals from the control group were used for bronchoalveolar lavage.

-the dose dependant effects of E glass fibres are represented in the table below:

**TABLE 12.** Summary of histopathological findings as number of animals with given score at each postexposure interval

| Group | Group number | Number of animals (out of 5) with indicated lesion for postexposure interval | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 wk | | | | 7 wk | | | 14 wk | | |
| | | Very slight | Slight | Moderate | Total | Very slight | Slight | Total | Very slight | Slight | Total |
| Accumulation of fiber/particle-laden macrophages | | | | | | | | | | | |
| Control | 1 | 0 | 0 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| E-glass low | 2 | 5[b] | 0 | | 5[b] | 5[b] | 0 | 5[b] | 3 | 2 | 5[b] |
| E-glass medium | 3 | 1 | 4[a] | | 5[b] | 3 | 2 | 5[b] | 0 | 5[b] | 5[b] |
| E-glass high | 4 | 0 | 5[b] | | 5[b] | 1 | 4[a] | 5[b] | 0 | 5[b] | 5[b] |
| MMVF21 low | 5 | 5[b] | 0 | | 5[b] | 4[a] | 0 | 4[a] | 5[b] | 0 | 5[b] |
| MMVF21 medium | 6 | 3 | 2 | | 5[b] | 3 | 2 | 5[b] | 3 | 2 | 5[b] |
| MMVF21 high | 7 | 0 | 5[b] | | 5[b] | 2 | 3 | 5[b] | 1 | 4[a] | 5[b] |
| CMS | 8 | 2 | 3 | | 5[b] | 1 | 4[a] | 5[b] | 0 | 5[b] | 5[b] |
| Bronchioloalveolar hyperplasia | | | | | | | | | | | |
| Control | 1 | 0 | 0 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| E-glass low | 2 | 5[b] | 0 | | 5[b] | 4[a] | 0 | 4[a] | 2 | 3 | 5[b] |
| E-glass medium | 3 | 4[a] | 2 | | 5[b] | 1 | 4[a] | 5[b] | 1 | 4[a] | 5[b] |
| E-glass high | 4 | 2 | 3 | | 5[b] | 0 | 5[b] | 5[b] | 1 | 4[a] | 5[b] |
| MMVF21 low | 5 | 4[a] | 1 | | 5[b] | 2 | 0 | 2 | 5[b] | 0 | 5[b] |
| MMVF21 medium | 6 | 4[a] | 1 | | 5[b] | 4[a] | 1 | 5[b] | 2 | 3 | 5[b] |
| MMVF21 high | 7 | 0 | 5[b] | | 5[b] | 0 | 5[b] | 5[b] | 4[a] | 1 | 5[b] |
| CMS | 8 | 3 | 2 | | 5[b] | 1 | 4[a] | 5[b] | 1 | 4[a] | 5[b] |
| Microgranulomas | | | | | | | | | | | |
| Control | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| E-glass low | 2 | 5[b] | 0 | 0 | 5[b] | 4[a] | 0 | 4[a] | 3 | 2 | 5[b] |
| E-glass medium | 3 | 1 | 4[a] | 0 | 5[b] | 0 | 5[b] | 5[b] | 1 | 4[a] | 5[b] |
| E-glass high | 4 | 0 | 4[a] | 1 | 5[b] | 0 | 5[b] | 5[b] | 0 | 5[b] | 5[b] |
| MMVF21 low | 5 | 3 | 1 | 0 | 4[a] | 0 | 0 | 0 | 0 | 0 | 0 |
| MMVF21 medium | 6 | 1 | 4[a] | 0 | 5[b] | 5[b] | 0 | 5[b] | 2 | 0 | 2 |
| MMVF21 high | 7 | 0 | 5 | 0 | 5[b] | 0 | 5[b] | 5[b] | 1 | 4[a] | 5[b] |
| CMS | 8 | 4[a] | 1 | 0 | 5[b] | 1 | 4[a] | 5[b] | 0 | 5[b] | 5[b] |
| Interstitial fibrosis | | | | | | | | | | | |
| Control | 1 | 0 | 0 | | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| E-glass low | 2 | 5[b] | 0 | | 5[b] | 4[a] | 0 | 4[a] | 4[a] | 1 | 5[b] |
| E-glass medium | 3 | 5[b] | 0 | | 5[b] | 5[b] | 0 | 5[b] | 2 | 3 | 5[b] |
| E-glass high | 4 | 1 | 4[a] | | 5[b] | 0 | 5[b] | 5[b] | 1 | 4[a] | 5[b] |
| MMVF21 low | 5 | 5[b] | 0 | | 5[b] | 1 | 0 | 1 | 0 | 0 | 0 |
| MMVF21 medium | 6 | 5[b] | 0 | | 5[b] | 5[b] | 0 | 5[b] | 5[a] | 0 | 5[b] |
| MMVF21 high | 7 | 2 | 3 | | 5[b] | 2 | 3 | 5[b] | 2 | 3 | 5[b] |
| CMS | 8 | 5[b] | 0 | | 5[b] | 2 | 3 | 5[b] | 0 | 5[b] | 5[b] |

Note. Significance of difference in a pairwise Fisher's test compared to control group given as follows.
[a] $p < .05$.
[b] $p < .01$.

| RAC's response |
|---|
| As pointed out by Belgium, according to requirement in the CLP Regulation, Annex 1, Section 3.6.2.2.3.(b) "Carcinogenicity in experimental animals" it is possible to conclude:<br>"sufficient evidence of carcinogenicity if :<br>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<br>(a) two or more species of animals or<br>(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."

The experimental data for the E-glass microfibres clearly provide 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 exposure to E-glass fibres by the intraperitoneal route. This experimental evidence 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.

**Attachments:**

Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2 , submitted by:

- European Owens Corning Fiberglas SPRL on 18/04/2014 [file name:OC Comments to CLH consultation.pdf] [please refer to comment 1]
- PPG Industries Fiber Glass EMEA on 18/04/2014 [file name: 14-40-E-glass fibres of representative composition.pdf ][please refer to comment 2],
- Saint-Gobain ADFORS on 10/04/2014 [file name: Comments Substance Name E-glass fibres.pdf] [please refer to comment 3]
- P-D Glasseiden GmbH Oschatz on 11/04/2014 [file name: 2014-04-10_Comments to Proposal HCL E-glass Microfibers_P-D GSO_attachment.pdf] [please refet to comment 5]
- Johns Manville Europe GmbH on 16/04/2014 [file name: 2014 03 24 CLH Comments.pdf] [please refer to comment 7]
- GlassFibreEurope on 25/03/2014 [file name: 2014 03 24 CLH Comments.pdf] [please refer to comment 8]

Comments to the Harmonised classification and labelling proposal from France submitted by Johns Manville Europe GmbH on 16/04/2014 [file name: Comment_JohnsManville_e_glass_20130416.pdf] [please refer to comment 7]