Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

silicon carbide fibres (with diameter < 3 µm, length > 5 µm and aspect ratio ≥ 3:1)

EC Number: 206-991-8

CAS Number: 409-21-2; 308076-74-6

CLH-O-0000001412-86-200/F

Adopted

9 March 2018

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON SILICON CARBIDE FIBRES (WITH DIAMETER < 3 µM, LENGTH > 5 µM AND ASPECT RATIO ≥ 3:1)

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 comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. 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. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: silicon carbide fibres (with diameter <3 µm, length > 5 µm and aspect ratio ≥ 3:1)
EC number: 409-21-2; 308076-74-6
CAS number: 206-991-8
Dossier submitter: Netherlands

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	Germany	Kennametal Inc.	Please select organisation type..	1
Comment received				
Kennametal is a global producer of tooling. In response to the 2017 Public Consultation on the Netherlands proposal for Harmonised Classification and Labelling (CLH) for Silicon carbide whiskers, Kennametal is submitting the following information for your consideration. Silicon carbide fibres are never used as a standalone material. They are always mixed into other materials, typically and in our case into ceramics. Once the fibres are mixed and wetted or attached to other materials, any airborne risk is eliminated. In addition, SiC fibres are a niche material, with very limited use globally. We do consume less than 1 ton per year in the European Union. In general we agree and support the position and substantiation of Haydale Technologies, our supplier of this material.				
Dossier Submitter's Response				
See response to comment 10.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
25.04.2017	France		MemberState	2
Comment received				
Two CAS numbers: 409-21-2 (without specification of the form) and 308076-74-6 (fibres) have been found for silicon carbide. Could you please clarify why these CAS numbers cannot be taken into account in the future entry in Annex VI?				
Dossier Submitter's Response				
We did not take into account the CAS number 409-21-2 as the classification with Carc. 1B –				

H350i is warranted for all forms of SiC fibres fulfilling the WHO fibre definition (WHO, 1985) and not for non-fibrous forms. CAS number 308076-74-6 which is specific for fibres and could be considered to also contain whiskers and certain cleavage fragments could be considered for inclusion in a future entry in Annex VI.
RAC's response
The information concerning the entry has been considered in the opinion.

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	Germany	FEPA	Industry or trade association	3
Comment received				
FEPA disagrees with the conclusions of the CLP document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment FEPA comments Sic-fibres.docx				
Dossier Submitter's Response				
The FEPA document states that FEPA does not agree with the proposal to classify SiC cleavage fragments as they produced negative results in all testing importantly including the serosa test. We have long doubted as the available data does not allow making a precise definition of carcinogenic and non-carcinogenic SiC fibre sizes especially because all tests were performed with fibres with a large variability. Some carcinogenicity studies with non-fibrous forms were negative but most studies with fibrous forms including fibres smaller than 5 µm were positive. However due to the large variability it does not exclude the possibility that the larger fibre (>5 µm) contribute mainly to the carcinogenicity. Recent reviews suggested maximal diameter and length for mesotheliomas is < 0.1 µm and > 5 µm and for lung carcinoma 0.1 – 3 µm and > 15 µm (Lippmann, 2014, Harrison, 2015). In relation to fibres which cannot be completely taken up by macrophages resulting in frustrated phagocytosis, release of ROS and growth factors and secondary effects which may result in carcinogenesis, Lippmann (2014) considered a threshold of frustrated phagocytosis of the fibres at the stomata of 5 µm which can result in local effects including mesothelioma. Lippmann (2014) reviewed the available data and suggested critical minimal fibre lengths of 2 µm for fibrosis, 5 µm for mesothelioma and 15 µm for lung cancer. The related predominant diameters were > 0.15 µm, > 0.15 µm and < 0.1 µm respectively. More in general, fibres with a diameter above 3 µm are not considered respirable (Harrison, 2015). Overall this could be translated into a maximal diameter of 3 µm and a minimal length of 5 µm. Seen the resemblance of the effects of SiC fibres with other fibres, the use of the same fibre definition as for other fibres is justified. The serosa test (we assume this is Pott, 1994 in combination with Rodelsperger and Bruckel 2006), shows that the potency of cleavage fragments is lower than whiskers. This is also in line with the general knowledge on fibres that the carcinogencity increases with fibre length. However, this study does not show the absence of a carcinogenic effect of the cleavage fragments because the applied dose levels of the cleavage fragments were much to low to come to such a conclusion.				
RAC's response				
Rödelsperger and Brückel (2006) indicated that granular SiC may contain cleavage fragments with WHO fibres dimensions (< 3 µm diameter, > 5 µm lengths, aspect ratio of 3:1) but at a lower fraction, with a low fraction of fibres with diameters below 1 µm and no fibres longer than 10 µm. The concern relating to the SiC cleavage products has been				

considered in the opinion.

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	United States	Haydale Technologies Inc.	Company-Manufacturer	4
Comment received				
We do not object to the toxicology data presented in this report. The safety profile of pure SiC fibres is well-understood. However, this toxicology data is based in raw silicon carbide fibres as a standalone material. In-use, SiC fibres are always mixed with other materials. There are no known applications where SiC fiber exists in the neat state. SiC fibres are used as reinforcing agents in ceramics and plastics and are never used pure. When SiC fiber is mixed in with other matrix materials, the surface of the SiC becomes wetted and encumbered. This effect prevents the SiC fibres from becoming airborne. Therefore, mixtures of SiC fiber contain no airborne constituents and no respirable materials. Therefore, while we make no objections to pure SiC fibres, we believe it is factually incorrect and misleading to label products that contain SiC fibres in mixtures as potentially carcinogenic (H350i). ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comment on CLH Report for SiC Fibers.pdf				
Dossier Submitter's Response				
Please see our reponse to comment 10.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	Germany		MemberState	5
Comment received				
We agree to the CHL proposal regarding the classification of silicon carbide fibres as carcinogenic (Cat. 1B). - General comments on the information provided in the CLH-Report: * it is not obvious whether the studies mentioned in tables (and text) are performed according to or similar to any validated test guideline and/or whether it is a GLP study or not. * It is not clear from the table headlines, how the data in the tables was arranged (e.g. 1. route of administration, 2. species used,…). * Part A, Section 2.2, page 7 and 8: WHO definitions of whiskers and cleavage fragments admittedly are somehow covered by the WHO definition of fibres (< 3µm, longer than 5µm and aspect ratio > 3), however, the specific definitions of those forms differ. Thus, the definitions of the forms proposed for classification (fibres, whiskers, cleavage fragments) should have been reported in this paragraph. It is not clear from this paragraph why a CLH proposal is only necessary for "Silicon Carbide, (fibres fulfilling the WHO definition: diameter <3 µm, length > 5 µm and aspect ratio ≥ 3:1)" and not necessarily and specifically for the other two forms, too. The following references examining further parameters of SiC fibres might be helpful in this				

context (Gunnaes et al. (2005) Morphology and structure of airborne β-SiC fibres produced during the industrial production of non-fibrous silicon carbide. Journal of Materials Science 40, 6011-6017. Cheng et al. (1995). Silicon carbide whiskers: Characterzation and aerodynamic behaviors. Am. Ind. Hyg. Assoc. J. 56:970–978. Strom and Yu (1994) Mathematical Modeling of Silicon Carbide Whisker Deposition in the Lung: Comparison Between Rats and Humans. Aerosol Science and Technology 21(3), 193-209.)
* Part A, Section 2.4.1, page 8: First paragraph: the organ that is mentioned in the C&L inventory to be affected by single/repeated exposure to silicon carbide fibres is not specified.
* Part B, table 9, page 15 and 16: Is there any information about the physico-chemical properties of SiC fibres, whiskers and/or cleavage fragments specifically?
* Part B, page 18, last paragraph: the expression "more longest SiC fibres were present in the lung tissues" is unclear.
* Part B, section 4.1.3, page 19: "There was a lower retention of fibrous SiC or quartz compared to higher retention of angular (non-fibrous) SiC in sheep model of pneumoconiosis…." apparently means "There was a lower retention period of fibrous SiC or quartz compared to the retention period of angular (non-fibrous) SiC in sheep model of pneumoconiosis."
* Part B, section 4.1.3, page 19: the expression "the half-life of decrease" is unclear.

- General comment concerning labelling elements:

The classification of the substance as Carc. 1B, H350i would result in the pictogram GHS08 (not GHS05). The wording of the H350i is: May cause cancer by inhalation.

- General comment concerning substance identity:

On the front page of the CLH report the rows regarding the EC number, CAS number and Index number are left empty. In order to make clear, that these rows are intentionally left empty the information "not applicable" or (as done in Part A, section 1.1, table 1 of the CLH report) "none" would be appropriate. The same applies to the corresponding rows in Part A, section 1.1, table 1 of the CLH report (EC number and CAS number) respectively in Part B, section 1.1, table 1 of the CLH report (EC number, CAS number (EC inventory), CAS number, CAS name, IUPAC name and CLP Annex VI Index number).
Concerning Part B, section 1.1, table 1 of the CLH report we would like to mention that the name "Silicon Carbide (fibres fulfilling the WHO definition: diameter <3 µm, length > 5 µm and aspect ratio ≥ 3:1)" is given as EC name. Since this name does not correspond to an EC entry (EC number is intentionally left out), the row relates to a "common name" or "chemical name".

Dossier Submitter's Response

Thank you for the support for the proposed classification.

- General comments on the information provided in the CLH-report:

* For all references mentioned in tables 10, 11, 14, 15 and 36 GLP is not specified. In addition, no studies were claimed to be performed according to OECD accepted protocols.

* The comments are noted. However, the CLH report file cannot be updated anymore at this stage of the CLH-process. All information is included in the tables and conform the CLH report format. However, no consistent order was applied within the provided tables.

* In our opinion, the available data justify classification of SiC for all forms (fibres, whiskers and cleavage fragments) that fulfill the WHO definition of fibers. As there are no formal definitions of whiskers and cleavage fragments, but there is a definition of fibers, these three forms of SiC were all considered to be fibres. Therefore, the proposed entry for Annex VI covers fibers, whiskers and cleavage fragments fulfilling the WHO definition for fibres. The provided references do not provide a clear definition of the different types of SiC. Also it can be questioned whether airborne SiC whiskers collected during production via the Acheson process (Gunneas et al., 2005) are representative of the form present in the marketed and used form of SiC granulate due to the post production changes. The publication by Cheng (1995) provides some information on the relation between physical dimensions and aerodynamic dimensions of a specific type of SiC whiskers. However, it is difficult to extrapolate this information to whiskers in general. The publication by Strom and Yu (1994) provides information on the efficienty of lung deposition of SiC fibers of different dimensions in humans and rats based on theoretical models. The model was specific for SiC fibers due to the use of the density of SiC of 3.2 g/cm^3. As expected the results of the calculations shows that deposition in the alveolar region increases with smaller diameter and smaller length. The deposition in the alveolar region which is considered relevant for the carcinogenicity of the fiber size according to the WHO definition (3 µm diameter and 5 µm length) was calcullated at 3% in humans and 0.3% in rats. This shows that a small fraction of the WHO size fibres can reach the alveoli and that lung distribution is not the limiting factor for definition of the fibre dimension for the substance for carcinogenicity because the criteria do not take potency into account. *The organ that is mentioned in the C&L inventory to be affected by single/repeated exposure to silicon carbide is the lung. *No information on the physical-chemical properties is available from for example REACH because fibers/whiskers are not (yet) registered. However, some information is already available from public sources in chapter 1.1. Some further information is also available in the recently published IARC monography. However, the limited information available also to IARC indicates that such data is not publically available. * In the study of Davis and co-workers (Davis J.M.G. et al., 1996) SiC fibre durability was examined both in vivo and in vitro. It was found that compared to microfibres mainly the longest SiC fibres were present in the lung tissues. * Although we agree with the proposed sentence, a CLH dossier cannot be changed after submission. * Assuming a one component exponential decrease, the half-life of decrease of concentration in lung lavage fluid would be 5.8 months for angular particles and 1.7 months for fibres (Dufrense A. et al. 1992). - General comment concerning labeling elements: * Indeed we have made a mistake. The pictogram should be GHS08 insteat of GHS05. The wording of the H3501 is: May cause cancer by inhalation, insteat of may cause cancer via inhalation. Although we agree a CLH dossier cannot be changed after submission. - General comment concerning substance identity: * We agree that it would have been clearer if we mentioned in the rows which are intentionally left empty the information "not applicable"or "none". * We agree that "Silicon Carbide (fibres fulfilling the WHO definition: diameter <3 µm, length > 5 µm and aspect ratio ≥ 3:1)" is no EC name and it would have been clearer if we would have mentioned the name in the row related to a "common name" or "chemical name".
RAC's response
The answers were noted/considered.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON SILICON CARBIDE FIBRES (WITH DIAMETER < 3 µM, LENGTH > 5 µM AND ASPECT RATIO ≥ 3:1)

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	Germany	Kennametal Inc.	Please select organisation type..	6
Comment received				
We do note that silicon carbide is chemically inert, is not bioactive, is not cytotoxic or sensitizing, has no negative environmental impact. We do accept and work accordingly that silicon carbide whiskers are carcinogenic because of the fiber dimensions. They are always mixed with other materials. SiC Whiskers are never used alone, always mixed with other materials where the fibres no longer become airborne. Therefore, any health effect associated with airborne materials is eliminated. It is factually incorrect and misleading to classify and label products containing SiC Whiskers with H350i, since the fibres cannot become airborn and therefore pose no health risk.				
Dossier Submitter's Response				
Please see our reponse to comment 10.				
RAC's response				
The provisions of the CLP Regulation on carcinogens in mixtures need to be considered.				

Date	Country	Organisation	Type of Organisation	Comment number
25.04.2017	France		MemberState	7
Comment received				
1. We question if the restriction to SiC fulfilling WHO definition is adequate. Indeed, it seems that carcinogenic effects have already been reported with SiC having a length less than 5 µm (Johnson et al. 1996; Miller et al. 1999b and Pott, 1991). In addition, according to the table 17 on page 49, long biopersistence is also expected with short length SiC fibres (no significant difference reported between the length > 0.4 or > 20 µm: 52.6 and 59.2% of biopersistence). It is noted that a negative result was observed in the 1-year inhalation study by Akiyama 2007 with fibres shorter than OMS definition. However, the negative result may also be explained by other parameters such as low exposure and small size groups. In addition, some studies identify that fibre length is not the only parameter explaining the effect (Johnson 1996). 2. We agree that grain SiC should not be classified. Nevertheless, we would like to note that carcinogenicity studies available with non-fibrous SiC were only performed by intraperitoneal route (no inhalation studies) that is maybe not a relevant route for non-fibrous SiC. Indeed, mesotheliomas are not expected with granular particles (rather lung tumours after inhalation). Overall, taken into account the overall data presented in this CLH report on granular SiC, we agree not to include this form in the classification proposal. 3. We agree to restrict the proposal to the inhalation route based on the mode of action. However, additional data on potential absorption via oral and dermal routes would be useful to confirm the lack of carcinogenicity expected by these routes in the absence of carcinogenicity studies. 4. In addition to length and diameter, the rigidity is an important parameter to take into account in the potential of fibres to induce mesothelioma. Do you have this type of information that may explain the difference of toxicity between fibres and whiskers? 5. The experimental database for whiskers clearly indicates that whiskers are carcinogenic in animals and we therefore considered that the criteria for classification 1B are fully met on				

this basis. Since whiskers SiC seem to have a similar aspect and toxicity as asbestos, we wonder if we can go further and conclude that SiC whiskers are carcinogens in humans (1A) even in absence of adequate human data? It is noted that in several studies the incidence of tumours was higher with SiCW than amosite and the delay for tumour induction shorter. They also exhibit similar biopersistence (Table 17) and similar pattern of effects in vitro inflammatory and oxidative reactions (Bruch 2014, Svensson 1997, Vaughan 1991), which are key parameters to understand the carcinogenic potential of a fibre.

6. Could you please clarify the material tested in the Stanton (1981) study? On page 43, "SiC fibres" are reported although on page 52, it is stated that it was "metallic crystalline whiskers".

7. We question on the adequacy of the proposal Carc 1B for SiC fibres. Indeed, based on the data presented in the CLH report, no carcinogenicity study seems to be available with this form (tested material in Stanton (1981) study to be clarified). Epidemiological data do not allow concluding on a relationship between tumours and SiC fibres mainly due to co-exposure, although the study Bugge 2012 identified that both cristobalite and SiC fibre contribute to the excess of lung cancer risk observed in the cohort. Experimental data are very scarce on the fibres and seem to indicate lower although not inexistent effects in vivo (Begin 1989, Bruch 1996) and in vitro (Bruch 2014) In this context, a Carc. 2 for SiC fibres would be maybe more appropriate. To support a classification Carc 1B for fibres, a comparison of structural and physicochemical properties between whiskers and fibres is needed to strengthen the rationale of similarity between fibres and whiskers.

Dossier Submitter's Response

1. We have long doubted as the available data does not allow making a precise definition of carcinogenic and non-carcinogenic SiC fibre sizes especially because all tests were performed with fibres with a large variability. Indeed results from studies evaluating carcinogenic effects of SiC fibres/whiskers with a mean length < 5µm (e.g. Pott, 1991; Johnson and Hahn, 1996; Miller et al., 1999b). However due to the large variability it does not exclude the possibility that the larger fibre (>5 µm) contribute mainly to the carcinogenicity. We agree that although fibre dimensions are a critical factor for carcinogenesis the results of Johnson N. F. and Hahn F.F. (1996) indicate that other aspects of a fibre must also be important. Recent reviews suggested maximal diameter and length for mesotheliomas is < 0.1 µm and > 5 µm and for lung carcinoma 0.1 – 3 µm and > 15 µm (Lippmann, 2014, Harrison, 2015). Overall this could be translated into a maximal diameter of 3 µm and a minimal length of 5 µm. Seen the resemblance of the effects of SiC fibres with other fibres, the use of the same fibre definition as for other fibres is justified.

2. Thank you for your support.

3. Thank you for your support. We agree that there are no studies available by dermal and oral route and that data on potential absorption via oral and dermal routes would be useful to confirm that no carcinogenicity via other relevant routes is expected. However, to our knowledge such data is not available. However, it should be considered that inhalation of fibres also result in oral exposure due to the transport of fibres in the airways to the gastro-intestinal tract. As known this has not resulted in tumour formation. Also in line with other insoluble fibres no oral and dermal absorption is expected. Further, local carcinogenicity after dermal and oral exposure is also not expected based on similarity with other nonsoluble fibres.

4. SiC fibres and whiskers have a high rigidity seen the high elastic modulus of approximately 350 GPa of a particular form of SiCW (CLH report page 11) and the use of

fibres and whiskers for the reinforcement of materials.

5. Read-across from fibres inducing mesotheliomas in humans towards SiC fibres based on comparable biopersistance, dimensions and supported by in vitro and in vivo results is supporting the classification based on the available animal data. However, classification in category 1A based on read-across is considered incorrect as category 1A should be restricted for substances which showed an increase in carcinogencity in humans and should not be based on read-across.

6. Thank you for pointing out the inconsistency. Stanton et al., 1981) used silicon carbide (si carbide) of one metallic crystalline whisker other than alumin as prepared by the General Technologies Corporation. Silicon carbide was a single sample, which was of exceptionally fine, uniform dimension.

7. As also stated in our reaction to comment 5 the available physico/chemical information is limited. The information present in the CLH proposal, SiCMa final Sic-fibres comments and the IARC monograph are provided in the table below.

Property	SiC whiskers	SiC fibres	SiC particles
Crystalline structure	Beta	Beta (most)	Alpha
Mono or poly crystalline	mono	Mono and poly	poly
Water and acid solubility	Insoluble	Insoluble	Insoluble
Dimensions	Variable but in general longer then 10 µm with a diameter below 1 µm	Not specified but the general fibre definition is a ratio between length and diameter above 3. Commercially available fibres may have diameters clearly above the WHO definition.	Mainly non-fibrous but containing some fibres and cleavage fragments fulfilling the fibre and the WHO definition depending on production and sorting

The table shows that the differences between whiskers and fibres are mainly in the dimensions of the fibres. As it is suggested to specify the dimensions in the Annex VI entry both whiskers and fibres fulfilling these criteria should have the same classification (Carc 1B). A justification for extrapolation from whiskers to fbres and cleavage fragments present as unintended by products in the Acheson process is more difficult. However, as both alpha and beta cristals are insoluble and the difference between mono and poly cristals is mainly that poly cristals can split into fibres with a smaller diameter whereas mono cristals more often break into shorter fibres, no difference in behaviour and carcinogenic potential can be expected based on the general knowledge on fibre carcinogenicity. Therefore, classification is also warranted.

RAC's response

The comments were taken into consideration in the opinion.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON SILICON CARBIDE FIBRES (WITH DIAMETER < 3 µM, LENGTH > 5 µM AND ASPECT RATIO ≥ 3:1)

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	Germany	FEPA	Industry or trade association	8
Comment received				
The conclusions on the carcinogenity of SiC cleawage fragments and short fibres are not justified scientifically. ECHA note – An attachment was submitted with the comment above. Refer to public attachment FEPA comments Sic-fibres.docx				
Dossier Submitter's Response				
See respons to number 3.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	Germany	SiCMA	Industry or trade association	9
Comment received				
Within our attached scientific document we come to the conclusion that further differentation for particles is required and the conclusions of the CLP dossier related to carcinogenicity need to be changed. This is supported by major scientist in this field. ECHA note – An attachment was submitted with the comment above. Refer to public attachment SiCMa final Sic-fibres comments.docx				
Dossier Submitter's Response				
Thank you for supporting our conclusion that certain forms of SiC fibres require classification as carcinogenic 1B and that a defintion of such fibres is required. From your comments, it is clear that SiCMa does not agree with the harmonized classification as proposed for cleavage fragments and short fibres. Several arguments for your position are given that only SiC whiskers (diameter < 1µm, length > 10µm; aspect ratio > 10) may be considered carcinogenic. The first argument is that cleavage fragments and fibres present as unwanted byproducts during the production of granular SiC have an alpha crystalline structure whereas the SiC whiskers which tested positive have a beta crystalline structure. We agree that there is a difference in crystalline structure. However, both crystalline structures are rigid and insoluble in water and acid. As the lung carcinogenicity of fibres is mainly determine by dose, dimensions and durability (Bernstein, 2007). As no difference in durability can be expected, no large difference in carcinogenic potency of alpha and beta SiC fibres of the same dimension is to be expected. As the criteria for classification do not take into account the potency, even a larger difference in potency is not relevant for classification. We also agree that cleavage fragments are polycrystalline whereas the tested whiskers are most likely monocrystalline (often not stated). However, as polycrystalline fibres will split along the long axis resulting in a decrease in diameter but not a decrease in length. This will make these fibres more toxic. Monocrystalline fibres will break reducing the length but not the diameter. This will reduce the toxicity. Therefore, the difference in mono or poly crystalline form will not decrease the concern for polycrystalline fibres. We agree that the dimension differ between cleavage fragments and the tested SiC				

whiskers. This difference has to be taken into account in the definition.

We do not agree with some of the statements made regarding the limitations of the animal studies (chapter 2.3). The statement that the study by Davis et al (1996) was negative for mesotheliomas is incorrect. The result was positive for SiC whiskers. Also the statement that the animals in this study were overloaded is not substantiated. Further, extrapolation from ip studies to inhalation studies for fibre carcinogenicity has been accepted as negative IP measurements are accepted as evidence for the absence of fibre carcinogenicity (CLP Annex VI 1.1.3.1 note Q.

The study by Rodelsperger (2006) indeed shows that cleavage fragments have a lower potency than whiskers for the induction of ip mesotheliomas. However, this study does not show the absence of a carcinogenic potential as the dose of cleavage fragments was much too low to conclude on the absence. The same argument applies to the other examples. Only a study containing a high dose of cleavage fragments or fibres with the WHO dimensions, would allow a conclusion on the absence of a carcinogenic potential. The study by Miller showed that the optimum relation between fibre length and peritoneal cavity mesotheliomas is for fibres with a length above 10 µm. However, this does not allow the conclusion that fibres with a length below are not carcinogenic. Overall, there is no compelling evidence showing that carcinogenetic cannot occur at fibre lengths below 10 µm or with a ratio below 10.

With regard to the epidemiologic studies (chapter 3) by Bugge, we agree that these are not providing clear evidence. This is also shown in the summary of the study (page 77) and by the fact that the results with not used as supportive evidence for cat 1B. The Wegman and Eisen (1981) study and some comparable studies were not considered relevant for assessment in line with the IARC assessment (IARC monograph 111). The study by Boffetta and Hashim (2016) could not have been included as this study was not available when the dossier was prepared. IARC concluded that there was a positive association between exposure to fibrous SiC and lung cancer (2017).

The other relevant studies not taken into account in the CLH report (chapter 5) are on the general relation between fibre dimensions and carcinogenicity. These studies are not specific for SiC. However, most studies focussed on the determination of the best correlation. However, for the definition for classification the question should be what the smallest particle size should be that could still induce carcinogenicity. We agree with the statement that the available information does not allow such conclusion due to the lack of tests with well-defined test samples. The approach based on mechanistic information such as proposed by Lippmann, 2014 and Harrision, 2015 is therefore the best available.

Chapter 6: Deficits related to correctness and completeness
We agree that the statement on the dimensions in the Rodelsperger and Bruckel study (2006) is misleading (although correct). However, the absence of a remark whether study was positive or negative is considered correct as no new in vivo study was performed in this publication. As a standalone study with only cleavage fragments the study would have been unacceptable due to the low dose.

With regard to the summary of the study by Davis et al (1996), it is stated that the length was above 5 µm.

Pott, 1991: Information on the median fibre size is available in Table 3 on page 553.

No conclusion that fibres with a length below 10 µm show no activity in the peritoneal test

was present in the paper by Miller et al (1999).

The comment regarding the publication by Roggli is unclear.

With regard to the comments on the reviews by Lippmann (2014) and Harrison et al (2015) and especially the missed studies see our response to chapter 2.3. The reasoning for the upper diameter limit is provided on page 675 of the publication by Lippmann and is mainly based on the ability to penetrate the lung as there was no upper value for the induction of lung cancer by fibres longer than 10 µm.

We have long doubted as the available data does not allow making a precise definition of carcinogenic and non-carcinogenic SiC fibre sizes especially because all tests were performed with fibres with a large variability. The inhalation study of Davis et al. (1996) (key study) is of highest interest showing that SiCW fibres (mean diameter of 0.45 µm and > 5 µm in length) were able to cause lung tumours. In addition the observed mesotheliomas point to the fact that the fibres were translocated from the alveolar region via the interstitium to the pleura. This confirms the carcinogenic potential known from other fibres fulfilling the WHO definitions after intrapleural or intraperitoneal injection. Indeed other results from studies evaluating carcinogenic effects of SiC fibres/whiskers with a mean length < 5µm (e.g. Pott, 1991; Johnson and Hahn, 1996; Miller et al., 1999b). However due to the large variability it does not exclude the possibility that the larger fibre (>5 µm) contribute mainly to the carcinogenicity.
Recent reviews suggested maximal diameter and length for mesotheliomas is < 0.1 µm and > 5 µm and for lung carcinoma 0.1 – 3 µm and > 15 µm (Lippmann, 2014, Harrison, 2015). In relation to fibres which cannot be completely taken up by macrophages resulting in frustrated phagocytosis, release of ROS and growth factors and secondary effects which may result in carcinogenesis, Lippmann (2014) considered a threshold of frustrated phagocytosis of the fibres at the stomata of 5 µm which can result in local effects including mesothelioma. Lippmann (2014) reviewed the available data and suggested critical minimal fibre lengths of 2 µm for fibrosis, 5 µm for mesothelioma and 15 µm for lung cancer. The related predominant diameters were > 0.15 µm, > 0.15 µm and < 0.1 µm respectively. More in general, fibres with a diameter above 3 µm are not considered respirable (Harrison, 2015).
Overall this could be translated into a maximal diameter of 3 µm and a minimal length of 5 µm. Seen the resemblance of the effects of SiC fibres with other fibres, the use of the same fibre definition as for other fibres is justified.

RAC's response

The rapporteurs acknowledge the detailed responses of the DS that clearly documented that different fibre types are responsible for different carcinogenic effects in the lung and the pleura. Some additional remarks:
To point IV) in the attachment: The commenter required that short fibres < 10 µm length should not be classified.
Based on the persistence of short fibres in the lung and their potential to translocate to the alveolar interstitium and pleura, there is no evidence to support this idea. As to the opposite, the Davis study supports that fibres < 10 µm induce lung carcinoma and mesotheliom and the Akiyama study demonstrated that only very short fibres (< 2 µm) were cleared from the lung, while those > 2 µm persisted.
Concerning point 2): To the understanding of RAC, the SiC fibre exposure in the study of Bugge *et al*. (2012) was not defined as exposure to whiskers only. The study of Bruch *et al*. (2014) performed *in vitro* tests on alveolar macrophages only, which is only one of many cells types affected.
As for asbestos, the effects of SiC fibres are not proposed by the DS to be determined by the fibre length only. Comparison with asbestos as positive control in the inhalation study of

Davis *et al*. (1996) may indicate that SiC whiskers may have a stronger potency. Concerning point 2.3): Overload is not relevant for the fibre-related development of lung cancer and even less for inhaled fibres that are transported into the pleural space. The i.p. testing is an accepted tool to identify fibres that cause mesotheliomas from those that do not. For SiC we do have the rare situation that studies for inhalation and after i.p. administration do consistently cause mesotheliomas. The positive inhalation test support the strength of the tumour response.

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	United States	Haydale Technologies Inc.	Company-Manufacturer	10

Comment received

In use in all known applications, there is no airborne SiC and thus no carcinogenicity issue. Therefore we believe it is factually incorrect and misleading to require products (such as ceramics or plastics) mixed with SiC fibres to be labeled as a potential carcinogen.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comment on CLH Report for SiC Fibers.pdf

Dossier Submitter's Response

Thank you on the support of the toxicology profile of the material and the exposure information from mixtures containing SiC Whiskers. However, exposure is not evaluated in the CLH report. We understand your concern regarding the classification and labelling of mixtures but that is beyond the scope of the classification proposal.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	Germany		MemberState	11

Comment received

Tables: It would be helpful and easier to handle the tables if an additional column was introduced to table 10, 11, 14, 15, and 36 stating whether the tested substance(s) concur with the fibre definition used for classification purposes (and if not, which parameter(s) differ in what way).

Repeated dose toxicity, table 10, page 21, study of Begin et al. 1989: It is unclear what "pathological scores of disease" means.

Section 4.7.1.6, page 23, last paragraph (Begin et al., 1989): it is unclear where the fibres were retained in the tissue. Causing accumulation in the inflammatory cells, mainly macrophages, does not allow to allocate the response to the lung interstitial tissues or the alveolar regions. Has the production of fibronection and other growth factors been examined or assumed to happen?

Section 4.7.1.6, 26: "SCOEL/SUM/88": references in the reference list are missing.

Page 33: The sentence "Silicon carbide has proven to be one of the most carcinogenic fibres to be investigated in experimental pathology studies (Davis et al., 1996)" seems to be an overstatement. If this was the case, no further information would be necessary to be able to classify SiC fibres correctly. Also, this study did not use a control, which makes this statement even more questionable.

Page 33: "Within 24 hr of being added to cell cultures, many, perhaps a majority, of the whiskers …" - It is not clear if "perhaps a majority" is definitively known or just an assumption.

Section 4.10.1.2, page 47: In the study by Davis et al. (1996) pleural mesotheliomas (24 %) and also 12 % of adenomas were detected after 238 days of inhalative exposure and a following recovery period (only one exposure concentration was tested!). However, since no (clean-air) control group was used in this study, these results are difficult to assess. Not running a control treatment in parallel to an exposure treatment is a severe flaw in study design (Davis et al. 1996) and drastically diminishes the reliability of this study, although values of laboratory control animals of previous studies were mentioned. Only slight differences in environmental parameters can influence the outcomes of studies (even if conducted in the same laboratory under (seemingly) the same conditions), which is why a concurrent control group is essential for obtaining reliable results. Using this flawed study as the key study is questionable and has to be reconsidered.
It is noted that the period of exposure should normally be for a period of 24 months (OECD TG 451) and not 238 days.
Moreover, analysing only 4 animals (or is it 9? this is not entirely clear) per group directly after the exposure period for carcinogenicity/fibrosis examination further decreases the value of this study, due to the extremely low statistical power of such a small treatment group. (OECD TG 451: "A sufficient number of animals should be used so that a thorough biological and statistical evaluation is possible. Each dose group and concurrent control group should therefore contain at least 50 animals of each sex.").
It is unclear why the remaining animals that were left for their full life span died.
The study information in Table 15 refers to intratracheal injection which needs clarification with regard to whether the same animals of the main study were treated. Table 16 refers to lung adenomas and carcinomas which were not mentioned in Table 15.
Akiyama et al. (2007), on the other hand, used a valid negative control and no neoplastic lesions (but fibrotic changes in lungs) could be identified after one year of inhalative exposure and the follow-up period of 6 days and 12 months. The lack of tumour formation (and neoplastic lesions) in this study might have been due to the low exposure level (also here only one exposure concentration was tested!). In the study by Akiyama, broncho-alveolar hyperplasia formation with fibrous aggregations was observed in two animals of the exposed group which might be indicative of a pre-stage of tumour formation. Further, the parameter lung weight was significantly increased in the exposure group at all tested time points (3, 6 and 12 months).

Section 4.10.1.4, page 52, Table 19: It remains unclear how tumour probability was calculated. The percentages may be more informative.

Section 4.10.1.4, page 59, last paragraph: "Hence carcinogenicity mainly is restricted to a subgroup of WHO fibres longer than about 10 and thinner than about 1 µm."
Information is needed that this seems to be the case if such fibres were/are injected. This does not necessarily mean that the same outcomes can be expected after e.g. inhalation.

Section 4.10.3, page 74, last paragraph: Which fibres are concerned?: "Long fibres (> 20 µm)…"?, and in the same paragraph: "Short fibres (5 µm)" or "Short fibres (< 5 µm)", and in the same paragraph, page 75: "with smaller diameters (50 nm) being more toxic than wider diameter (150 nm)…" should this be < 50 nm and > 150 nm?

Section 4.10.4, page 75: We support that the inhalation study of Davis et al., 1996 is of highest interest showing that SiCW fibres were able to cause lung tumours. In addition the

observed mesotheliomas point to the fact that the fibres were translocated from the alveolar region via the interstitium to the pleura. This confirms the carcinogenic potential known from other fibres fulfilling the WHO definitions after intrapleural or intraperitoneal injection. Indications of fibre translocation to extrapulmonal tissues may be available in the study.

Section 4.10.4, page 75, second paragraph: "man" appears to be wrong, the context appears to refer to "rats".

Section 4.10.5, page 78, fourth paragraph: The criteria allow that the limited evidence of carcinogenicity from human studies may be considered as supporting Cat. 1B.

Section 4.10.5, page 79, second paragraph: a reference to "Consistent results (related to precursor findings and cell toxicity) are also shown by the in vivo repeated dose studies and the in vitro studies." is missing.

Section 4.10.5 and 4.10.6: Also results from studies evaluating adverse effects (carc.) of SiC fibres/whiskers with a mean length < 5µm or other differing (or not reported) parameters (e.g. Pott, 1991; Johnson and Hahn, 1996; Miller et al., 1999b; Adachi et al., 2001) are discussed. Are these fibre-/whisker-types, which do not conform to the WHO definition of fibres, to be included in the CLH proposal?

Section 4.10.5 and 4.10.6: "Only local tumours after inhalation, i.p. and intrapleural installation were observed indicating that the relevant route for carcinogenicity in the hazard statement could be limited to the inhalation route. There are no studies available by dermal and oral route. However, seen the proposed mechanism of SiC fibres and fibres in general for carcinogenicity after inhalation, no carcinogenicity via other relevant routes is expected." - It is problematic to argue that only local tumours after inhalation were observed, if one considers the mesotheliomas as a consequence of spreading of the fibres by interstitial pathways to neighboured tissues (pleura). Local to our interpretation should be related to the site of exposure only.
It needs to be reconsidered whether this information (or the lack thereof) is enough for proposing the hazard statement H350i and not H350. We propose to discuss whether there is any evidence from studies (on SIC fibres or comparable fibres) showing that uptake (and translocation) after oral exposure may be excluded.

Generally: It should be thought about considering the following studies, which are not yet mentioned in the CLH report but which might further support the proposed classification:
1) Cullen et al., 1997. Short-term Inhalation and in Vitro Tests as Predictors of Fiber Pathogenicity. EHP 105(5), 1235-1240.
2) Ogami et al. 2001. Short Term Effect of Silicon Carbide Whisker to the Rat Lung. Industrial Health 39, 175–182.
3) Ogami et al. 2007. Histopathological Changes in Rat Lung Following Intratracheal Instillation of Silicon Carbide Whiskers and Potassium Octatitanate Whiskers. Inhalation Toxicology (19), 753–758.
4) Strom and Yu 1994. Mathematical Modeling of Silicon Carbide Whisker Deposition in the Lung: Comparison Between Rats and Humans. Aerosol Science and Technology 21(3), 193-209.)
5) Brown et al. 1999.Induction of nuclear translocation of NF- κB in epithelial cells by respirable mineral fibres. Journal of Pathology 189, 258-264.
6) Hayashi et al. 1988. Silicon Carbide in Lung Tissue of a Worker in the Abrasive Industry. American Journal of Industrial Medicine 14(29), 145-155.
7) Bye et al. 1985. Occurrence of airborne silicon carbide fibres during industrial production

of silicon carbide. candinavian Journal of Work, Environment and Health11(2), 111-115.
8) Dion et al. 2005. Assessment of Exposure to Quartz, Cristobalite and Silicon Carbide Fibres (Whiskers) in a Silicon Carbide Plant. Ann. occup. Hyg. 49(4), 335–343.
9) Føreland et al. 2008. Exposure to Fibres, Crystalline Silica, Silicon Carbide and Sulphur Dioxide in the Norwegian Silicon Carbide Industry. Ann. Occup. Hyg. 52(5), 317–336.
10) Ishihara et al. 1998. Cellular biological effects and a single transtracheal injection test in three types of whisker fibres. Inhalation Toxicology 10(4), 275-291.
11) Shibata et al. 2007. Magnetometric evaluation of the effects of man-made mineral fibres on the function of macrophages using the macrophage cell line RAW 264.7. Industrial Health 45(3), 426-436.
12) Watanabe et al. 2000. Magnetometric Evaluation for the Effects of Silicon Carbide Whiskers on Alveolar Macrophages. Industrial Health 38, 239–245.

Dossier Submitter's Response

Thank you for your support. We agree that it would have been clearer if we added an additional column to the tables 10, 11, 14, 15 and 36 stating whether the tested substance(s) concur with the fibre definition used for classification purpose. However, the studies were performed with SiC having a range of fibre dimensions. The average or median fibre dimension is not a good descriptor of the dimensions because a small fraction of long and thin fibres could cause the observed effects whereas the average or median dimensions do not concur with the fibre definitions. Also the distribution of the fibre dimensions is not specified in the publication making it difficult to assess. If more detailed information on the diameter and length of the fibre in the test substance was available, this information is included in the table.

Regarding the "pathological scores of disease " by repeated dose toxicity, table 10, page 21, study of Begin et al. 1989: is meant the pathology of these groups at necropsy, eight months after exposure. The lung morphology of the sheep was normal in groups Sa and latex. The lung tissue of sheep in the graphite group, SiCp and SiCpa groups contained accumulation of particles mostly within macrophages in alveoli and interstitium without cellular reaction. In the SiCf, SiCfa and crocidolite group, the lung changes are characterized by a diffuse alveolitis with early nodular silicotic lesions.

Section 4.7.1.6, page 23, last paragraph (Begin et al., 1989) long fibres were retained in the lung tissue (not further specified). Lung lavage cellularity, biochemistry and culture data from sheep exposed to Sa, crocidolite, SiCf and SiCfa show the production of fibronection at 8 month was significantly increased, with some attenuation for the SiCf group, fibroblast growth activity was significantly increased in all fibre groups.

Our apologies that the reference SCOEL/SUM/88 (2012) is not included in the reference list. It is available at: ec.europa.eu/social/BlobServlet?docId=7722&langId=en.

We agree that the sentence in an overestimation and should be seen in the context of the study of Brown et al (1998). Davis et al. (1996) studied the effects of three types of mineral fibre, glass microfiber, SiCW and amosite. Lungs of rats treated with microfiber showed almost no fibrosis and the few benign tumors recorded were not significantly more than expected from control animals. SiCW produced slightly fewer tumors in the lung parenchyma than amosite but produced a total of 10 mesotheliomas compared to 2 with amosite.

It is not clear to us if "perhaps a majority" is meant as an assumption or as a definitively known. The results are not shown in the reference.

The inhalation study of Davis et al. (1996) (key study) is of highest interest showing that

SiCW fibres were able to cause lung tumours. In addition the observed mesotheliomas point to the fact that the fibres were translocated from the alveolar region via the interstitium to the pleura. This confirms the carcinogenic potential known from other fibres fulfilling the WHO definitions after intrapleural or intraperitoneal injection. The absence of a concurrent control group normally reduces the reliability. However, the presence of some information on historical control data showing low incidence plus the low incidence of carcinoma and mesothelioma in one of the exposed groups (microfibre) compared to the strong increase in the SiC exposed group provides sufficient information to consider that SiC induced a strong increase in tumour formation in this study. Further, pleural mesotheliomas occur rarely in rats and in humans (Blackshear, 2014, Tox. Path. 42(5): 863-876). According to table 3.3 of the IARC monography on asbestos (100c), no pleural mesotheliomas were observed in a range of rat strains.
The short exposure period of 238 days during 5 days a week meaning approximately 1 year is of concern when the carcinogenicity study is negative. However, as in this case a positive result was obtained this does not limit the reliability of the outcome.
Four animals per group were killed for pathology after 12 months and the remaining animals were left for their full life span. The cause of the spontaneous mortality is not reported. Again this would normally reduce the reliability of the study as rats spontaneously develop tumours. However, as pleural mesothelioma in the rat is rare, the strong increase in mesothelioma clearly shows the carcinogenic effect of SiC whiskers.
The publication by Davis et al (1996) contains both inhalation and ip studies which are summarised in chapter 4.10.1.2 and 4.10.1.4.

Indeed Akiyama et al. (2007) showed increased lung weight and fibrotic changes in lungs but no tumor induction. Akiyama et al. (2007) used SiCW with average length of 2.8 µm which does not fulfil the WHO definition. This inhalation study suggests that fibre characteristics is important for carcinogenesis of SiC fibres. The absence of lung tumours including mesotheliomas in this study confirms the low spontaneous incidence of this type of tumours in the rat.

Section 4.10.1.4, page 52, Table 19, the probability of pleural sarcoma in each experiment was calculated by an actuarial life table method that accounts for early deaths without pleural sarcoma and provides a means of making quantitative comparisons of one experiment with another. The percentages were calculated at 65% for the SiC group and 1.9% for the combined controls.

Section 4.10.1.4, page 59, last paragraph: we agree that it would have been clearer if we point out that this seems to be the case when injected. No information is available with fibres with exactly these dimensions.

Section 4.10.3, page 74, last paragraph: we agree with your suggested changes. Long fibres (length > 20 µm) are of concern as these cannot be completely taken up by macrophages resulting in frustrated phagocytosis, release of ROS and growth factors and secondary effects which may result in carcinogenesis. Short fibres (< 5 µm) are of no concern (except for overload) as a fraction of the inhaled fibres are transported by the draining lymphatic fluid into the pleural space. Further, the diameter is more important than length, with smaller diameters (<50 nm) being more toxic than wider diameter (>150 nm).

Section 4.10.4, page 75: thank you for your support.

Section 4.10.4, page 75, second paragraph: This sentence intent to state that the pleural carcinomas observed in rats resemble the mesenchymal mesotheliomas observed in humans. The sentence is considered correct but unclear.

Section 4.10.5, page 78, fourth paragraph, we agree that there is epidemiologic data showing limited evidence of carcinogenicity from human studies. However as confounding cannot be ruled out because there was also exposure to other carcinogens, the epidemiologic data is not suitable as supporting evidence for Carc 1B.

Section 4.10.5, page 79, second paragraph: Thank you for pointing out. The references to be included are Lapin CA et al, 1991; Bruch J. et al., 1993-2; Begin R et al., 1989, Bruch and Rehm, 1996; Bruch J. et al., 2014; Svensson I et al., 1997, Vaughan GL. et al., 1991.

Section 4.10.5 and 4.10.6: The available data does not allow making a precise definition of carcinogenic and non-carcinogenic SiC fibre sizes especially because all tests were performed with fibres with a large variability. It does not exclude the possibility that the larger fibre (>5 µm) contribute mainly to the carcinogenicity. Recent reviews suggested maximal diameter and length for mesotheliomas is < 0.1 µm and > 5 µm and for lung carcinoma 0.1 – 3 µm and > 15 µm (Lippmann, 2014, Harrison, 2015). Overall this could be translated into a maximal diameter of 3 µm and a minimal length of 5 µm. Seen the resemblance of the effects of SiC fibres with other fibres, the use of the same fibre definition as for other fibres is justified.

Section 4.10.5 and 4.10.6: We agree that there are no studies available by dermal and oral route. However, seen the proposed mechanism of SiC fibres and fibres in general for carcinogenicity after inhalation, no carcinogenicity via other relevant routes is expected. Therefore, classification with the hazard statement H350i is proposed. This is also in line with the RAC advice on E-glass and glass microfibers (RAC, 2014a and RAC, 2014b). We agree that it can be questioned whether mesothelioma should be considered local tumours. However, they can also not be considered systemic tumours because the mechanism for induction of mesothelioma is that they cannot pass the stomata meaning they cannot reach the general lymphatic system and after that the blood circulation.

Thank you for the supporting documents. In addition, the IARC monograph (111) is available containing background information on for example the production of the different forms of SiC.

1) Cullen et al., 1997. Short-term Inhalation and in Vitro Tests as Predictors of Fibre Pathogenicity. EHP 105(5), 1235-1240.

In this study a number of in vitro and short term in vivo parameters were compared for a number of fibres including SiC whiskers with the pathogenicity ranking in long-term experiments. It was concluded that only lung cell proliferation (BrdU) shows potential as a predictive measure.

2) Ogami et al. 2001. Short Term Effect of Silicon Carbide Whisker to the Rat Lung. Industrial Health 39, 175–182.

In this study the effect of tracheal installation and inhalation of SiC whiskers (mean 5.1 (SD 2.3) * 0.3 (SD 1.5) µm) on parenchymal inflammation was compared at several time points after the start of exposure. Inhalation induced less inflammation compared to intratracheal installation. However, the residual amount after inhalation was also lower than the installed dose. No pleural changes were observed in any group. The effect of the short fibres was considered limited.

3) Ogami et al. 2007. Histopathological Changes in Rat Lung Following Intratracheal Instillation of Silicon Carbide Whiskers and Potassium Octatitanate Whiskers. Inhalation Toxicology (19), 753–758.

This study determines the level of lung inflammation of 2 mg SiC whiskers (mean 5.1 (SD 2.3) * 0.3 (SD 1.5) µm) and other materials after a single intratracheal installation up to 6 months after installation. The highest level of inflammation of the parenchym was observed after 1 month and then decreased. The long term response was less than for crocodolite and crystalline silica. The effect of the short fibres was considered limited.

4) Strom and Yu 1994. Mathematical Modeling of Silicon Carbide Whisker Deposition in the Lung: Comparison Between Rats and Humans. Aerosol Science and Technology 21(3), 193-209.)
The publication provides information on the efficiency of lung deposition of SiC fibers of different dimensions in humans and rats based on theoretical models. The model was specific for SiC fibers due to the use of the density of SiC of 3.2 g/cm^3. As expected the results of the calculations shows that deposition in the alveolar region increases with smaller diameter and smaller length. The deposition in the alveolar region which is considered relevant for the carcinogenicity of the fiber size according to the WHO definition (3 µm diameter and 5 µm length) was calculated at 3% in humans and 0.3% in rats. This shows that a small fraction of the WHO size fibres can reach the alveoli and that lung distribution is not the limiting factor for definition of the fibre dimension for the substance for carcinogenicity because the criteria do not take potency into account.

5) Brown et al. 1999.Induction of nuclear translocation of NF- κB in epithelial cells by respirable mineral fibres. Journal of Pathology 189, 258-264.
This study indicates that in vitro NF-$_k$B nuclear translocation, as parameter for oxidative stress, can discriminate between carcinogenic fibres including SiC (65% above 10 µm length) and non-carcinogenic fibres. The mechanism via oxidative stress was confirmed by co-incubation with antioxidants. This study indicates that the induction of carcinogenicity by fibres can at least partially be explained by the induction of oxidative stress. SiC was the most potent of the tested fibres.

6) Hayashi et al. 1988. Silicon Carbide in Lung Tissue of a Worker in the Abrasive Industry. American Journal of Industrial Medicine 14(29), 145-155.
In this case study a worker in an abrasive factory plant developed pneumoconiosis. The total dust in the lung was high and contained 43% silicon carbide. This study shows the high retention of SiC in humans after inhalation exposure.

7) Bye et al. 1985. Occurrence of airborne silicon carbide fibres during industrial production of silicon carbide. Scandinavian Journal of Work, Environment and Health11 (2), 111-115.
This study shows the presence of SiC fibres during production of SiC including fibres fulfilling the WHO definition. The crystalline structure included several alpha types.

8) Dion et al. 2005. Assessment of Exposure to Quartz, Cristobalite and Silicon Carbide Fibres (Whiskers) in a Silicon Carbide Plant. Ann. occup. Hyg. 49(4), 335–343.
This study confirms that exposure to SiC fibres occurs during the production of SiC.

9) Føreland et al. 2008. Exposure to Fibres, Crystalline Silica, Silicon Carbide and Sulphur Dioxide in the Norwegian Silicon Carbide Industry. Ann. Occup. Hyg. 52(5), 317–336.
This study confirms that exposure to SiC fibres occurs during the production of SiC.

10) Ishihara et al. 1998. Cellular biological effects and a single transtracheal injection test in three types of whisker fibres. Inhalation Toxicology 10(4), 275-291.
In this study the in vitro and in vivo toxicity of SiC fibres was tested. Two months after a single intratracheal installation of 50 mg/kg bw SiC fibres (6.4 ± 2.5 * 0.3 ± 1.6 µm) inflammatory cells accumulated around the fibres and ingesting the whiskers. Slight fibrosis.

No clear correlation was found between the tested in vitro parameters and the in vivo results. 11) Shibata et al. 2007. Magnetometric evaluation of the effects of man-made mineral fibres on the function of macrophages using the macrophage cell line RAW 264.7. Industrial Health 45(3), 426-436. This study shows that SiC fibres (6.4 (SD 2.5) * 0.3 (SD 1.6) disturb the cytoskeleton of the cells of this murine macrophage cell line and that the fibres twined around and englobed the cells. 12) Watanabe et al. 2000. Magnetometric Evaluation for the Effects of Silicon Carbide Whiskers on Alveolar Macrophages. Industrial Health 38, 239–245. A number of parameters were determined and affected after exposure of Syrian golden hamster alveolar macrophages to SiC (6 * 0.3 µm). However, the relevance and the relation of the parameters with the in vivo toxicity of fibres are not clear. Overall, these additional publications do not give additional evidence for the carcinogenicity of SiC fibres or evidence contradicting this. Also the publications do not warrant a different definition of the fibres classified as carcinogenic category 1B. The exposure information confirms the relevance not only of the produced whiskers but also of other fibrous forms. The mechanistic information confirms the importance of the 3D theory.
RAC's response
The additional information is noted.

PUBLIC ATTACHMENTS
1. FEPA comments Sic-fibres.docx [Please refer to comment No. 3, 8]
2. SiCMa final Sic-fibres comments.docx [Please refer to comment No. 9]
3. Comment on CLH Report for SiC Fibers.pdf [Please refer to comment No. 4, 10]