National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

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RIVM Letter report 2015-0202
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Colophon

Bastiaan Venhuis (author), RIVM
Peter Keizers (author), RIVM
Robert Geertsma (author), RIVM
Marjolijn Woutersen (author), RIVM
Andre Muller (author), RIVM
Marja Pronk (author), RIVM

Contact:
Bastiaan Venhuis
GZB
bastiaan.venhuis@rivm.nl

This investigation has been performed by order and for the account of IGZ, MHRA, HPRA, FAGG-AFMPS

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National Institute for Public Health and the Environment
P.O. Box 1 | 3720 BA Bilthoven
The Netherlands
www.rivm.nl/en

Synopsis

Risk analysis of particulate contamination on Silimed silicone-based breast implants

Particles were found on Silimed silicone-based breast implants that should not be there. These included man-made mineral fibres, such as glasswool and rockwool. The risk to the health of people with such implants is minimal.

For this study, 39 breast implants were examined manufactured by the Brazilian company Silimed between 2009 and 2015. In addition, 12 breast implants from three other manufacturers were examined. Mineral fibres were also found on implants from one other manufacturer, but of a different type. Additional studies are necessary to assess the health risk analysis for those fibres.

The reason for this study was the suspension of the CE certificate for Silimed medical devices in September 2015. The manufacturer was unable to prevent contamination with mineral fibres. European medical device regulators consequently commissioned investigations to examine whether people with contaminated implants were at risk. A team of international medical experts will advise the European healthcare authorities on the implications of the findings for physicians and patients with such implants.

Keywords: Silimed, man-made mineral fibres, MMMF, risk assessment, rockwool, slagwool, glasswool, glass fibre, silicone-based breast implant, SBI, particulate contamination, medical device.

Publiekssamenvatting

Risicoanalyse van deeltjesverontreiniging op siliconen borstimplantaten van Silimed

Op siliconen borstimplantaten van de fabrikant Silimed zijn deeltjes aangetroffen die daar niet thuishoren. Het betreft onder meer minerale vezels van glaswol en steenwol. Het risico voor de gezondheid van mensen met deze implantaten is minimaal.

Voor deze studie zijn 39 borstimplantaten onderzocht van het Braziliaanse bedrijf Silimed, geproduceerd tussen 2009 en 2015. Er zijn ook 12 borstimplantaten van drie andere fabrikanten onderzocht. Op implantaten van één van de andere fabrikanten zijn ook minerale vezels aangetroffen, maar van een andere soort. Er is meer onderzoek noodzakelijk om de gezondheidsrisico's daarvan in te schatten.

Aanleiding voor dit onderzoek was de schorsing van het CE-certificaat voor medische hulpmiddelen van Silimed in september 2015. Het bedrijf bleek een verontreiniging met minerale vezels niet te kunnen voorkomen. Europese toezichthouders lieten vervolgens onderzoeken of mensen met verontreinigde implantaten risico lopen. Een internationale groep medische experts zal de Europese toezichthouders adviseren over wat de bevindingen van dit rapport betekenen voor artsen en voor patiënten met deze implantaten.

Kernwoorden: Silimed, minerale vezels, MMMF, risicobeoordeling, steenwol, slakkenwol, glaswol, glasvezel, siliconen borstimplantaat, SBI, deeltjesverontreiniging, medisch hulpmiddel.

Contents

1 Summary

In September 2015, a CE certificate covering Silimed medical devices was suspended for three months. This measure followed on Silimed being unable to resolve an issue of particulate contamination of their silicone breast implants (SBI). Reports by the notified body TÜV SÜD showed that particles had been found on several Silimed textured SBI, including particles described as 'glass fibres'.
RIVM started a study at the request of MHRA (United Kingdom), HPRA (Ireland), FAGG-AFMPS (Belgium) and IGZ (The Netherlands) to evaluate whether the presence of such fibres may pose a risk to the patient after implantation. This investigation comprised of a laboratory study on two Silimed SBI types plus SBI from three other manufacturers and a risk assessment. In order not to lose time, the risk assessment commenced with the data from the available reports. The laboratory findings were used to fine-tune the risk assessment, where necessary.

In the laboratory study 39 Silimed SBI, manufactured between December 2009 and August 2015 were examined. Using the TÜV SÜD experimental method, 'glass fibres' were found on SBI from all available years of manufacture. These fibres were identified as man-made mineral fibres (MMMF) based on their elemental composition. Contrary to earlier reports, the contamination with MMMF affected both textured and PU-coated SBI types. Two types of MMMF could be distinguished. There was no relation between the type of MMMF and the SBI type.
The numbers of MMMF found per implant by RIVM were similar to those reported by TÜV SÜD. However, TÜV SÜD reported finding a high number of 'small straight fibres' at the surface of Silimed textured SBI. These 'small straight fibres' were not identified in their study but might be MMMF fragments. In our study, no such small straight fibres were observed. On the PU-coated SBI, several other particles were found that were not described in earlier reports. These particles were tentatively identified as spherical glass, siliciumcarbide, and iron-rich particles. For comparison, 12 SBI from three other manufacturers were examined (4 SBI each). MMMF were not observed on Brand A and B SBI. However, MMMF of a third type were observed on 2 of the 4 Brand C SBI.

The risk analysis started with the data from the TÜV SÜD reports. In their reports, the chemical composition of the different types of MMMFs shows that on average, these fibres have the closest similarity to rockwool and/or slagwool fibres. The fibres vary in size, but have a median length of ~180 µm and a median diameter of 9 µm. The highest numbers of fibres were 73 MMMF per SBI and 1440 small straight fibres per SBI. With exception of the 'small straight fibres' these data are in line with the findings in the present laboratory study. A risk analysis was carried out for two scenarios. In the first scenario it was assumed that all 'small straight fibres' were MMMF. The resulting exposure of someone with two implants is up to $3*10^3$ fibres. This approach was used by Silimed in their risk analysis. In the second scenario, it was assumed that the 'small straight fibres' were not MMMF. The resulting exposure of someone with two implants is 146 fibres. In either scenario it was assumed that all MMMF were present on the implanted SBI and would

remain in the body after any implant removal. Both non-carcinogenic and carcinogenic endpoints were considered.

Foreign objects including fibres induce inflammation which in time can lead to the formation of fibrosis and incidentally granuloma formation. The toxic potential of fibres depends on their dose, dimensions, rigidity and durability. Depending on their specific characteristics fibres may induce what is now recognized as "frustrated phagocytosis" meaning that macrophages fail to incorporate and remove fibres, which results in a chronic persistent inflammation. Regular foreign body reactions with capsule formation can also be expected for the long fibres identified on the breast implants. The scientific committee on occupational exposure limits (SCOEL) derived an occupational exposure limit (OEL) of $3*10^7$ rock/slagwool fibres/day as protective limit for chronic lung inflammation and fibrosis. While this applies to inhalation and cannot be compared directly with the exposure to implanted fibres, it is safe to conclude that the fibre dose stemming from the breast implants is far below the limit that is considered acceptable for daily, lifelong occupational exposure. Thus, the likelihood that appreciable inflammation reactions will occur is very low.
The risk of carcinogenesis was calculated using various carcinogenicity studies with intraperitoneal exposure to rockwool fibres, which is the most potent type of MMMF. It was assumed the exposure occurs only once, but the fibres remain in the body for the entire lifetime. Using a non-threshold approach, this resulted in a cancer risk of 9 in 1,000,000 for exposure to $3*10^3$ fibres (scenario 1). When only the large fibres were considered in the risk assessment, the resulting cancer risk was 4.42 in 10,000,000 for 146 fibres (scenario 2). The cancer risk that is considered acceptable for lifetime exposure of the general population is usually 1 in a 1,000,000 which would be equivalent to 330 fibres.

Although the cancer risk calculated for the fibres stemming from the SBI is near the limit of acceptability, it should be stressed that this is based on worst case assumptions on both the hazard and exposure side (non-threshold approach, most potent type of fibre). Moreover, no epidemiological evidence for tumour formation after inhalation exposure to inhalable MMMFs was found.

The risk assessment contains a number of uncertainties, mainly because all identified toxicity studies used smaller, inhalable size MMMF and inhalation or intraperitoneal exposure, which is not directly comparable to implanted MMMF of much larger, non-inhalable size in breast tissue. The mechanism of toxicity of the implanted fibres is, however, similar to that of other fibres/foreign objects (frustrated phagocytosis and regular foreign body reactions with encapsulation). The actual risks are expected to be lower than the calculated risks.

2 Introduction

2.1 Initial information

On September 17th, 2015, the German notified body TÜV SÜD suspended the CE mark for Silimed products for three months. This step was taken after an issue of particulate contamination of Silimed products which was not resolved adequately. RIVM was informed about these events by the Dutch Health Care Inspectorate (IGZ) and received the following documents[1-4]:

1. TÜV SÜD document Silimed UAA 713061556 entitled “Summary of events regarding Silimed”, dated 23 September 2015. Received by RIVM on September 23rd, 2015.

2. TÜV SÜD Report UAA PS order number 713061556 / Industrie Service order number 600014710 entitled “Analysis of particulate contamination on textured, smooth, and polyurethane coated mammary implants”, dated 27 July 2015. Received by RIVM on September 23rd, 2015.

3. Robert Mathys Foundation (RMS) Report A15_0969_00 entitled “Residue Analysis on Mammary Implants and Tissue Expanders A Summary”, undated (study completed on 09 July 2015). Received by RIVM on September 23rd, 2015.

4. Silimed critical analysis ACR-116 entitled “Risk analysis to the patient due to the presence of particles on the surface of Silimed implants”, dated 4 September 2015. Received by RIVM on September 29th, 2015.

RIVM was asked by IGZ to take note of these reports, and to do an exploratory check for particles on the Silimed polyurethane (PU)-coated silicone-based breast implants (SBI) already present at RIVM, and to propose a strategy for health risk analysis to IGZ and inspectorates from other European countries. After a month, a fifth report was received[5]:

1. Exponent report entitled “Toxicological Risk analysis of Foreign Material Detected on SILIMED Silicone Breast Implants”, dated October 14th, 2015. Received by RIVM on October 22nd, 2015.

2.2 RIVM experience in SBI studies

RIVM is studying SBI on behalf of the Dutch Healthcare Inspectorate (IGZ), focussing on product file conformity of the silicone gel and the envelope. For that reason, RIVM was in the possession of 18 Silimed PU-coated SBI. In the course of the study, 10 Silimed PU-coated SBI had been opened for investigation of the gel and the envelope. At the time the CE certificate for Silimed was suspended, RIVM was investigating relatively high levels of cyclosiloxane impurities that were found in 1 of the 10 evaluated Silimed PU-coated SBI.

2.3 Exploratory assessment of the situation

The reports by TÜV SÜD and the RMS (a contract laboratory for TÜV SÜD) describe various particles found on the surface of smooth, textured, and PU-coated SBI and tissue expanders manufactured by Silimed. The reports were not entirely clear about the identity and source of the contamination. TÜV SÜD reported finding 'glass fibres' on Silimed textured SBI manufactured between 2013 and 2015. These particles were NOT reported for Silimed smooth and PU-coated SBI.

In addition to the particulate contamination, the RMS report describes relatively high levels of cyclosiloxane impurities that were found in 3 of the 3 evaluated Silimed textured SBI. Although elevated cyclosiloxane levels in the SBI gel do not present a significant health threat, their presence is not consistent with fully crosslinked silicone gel.[6, 7] During the present study, RMS withdrew their conclusion when it became apparent that the reported levels were actually very low. Therefore, cyclosiloxane levels are not addressed in this report. The increased levels found by RIVM earlier will be reported separately.

The remaining 8 sealed PU-coated Silimed SBI at RIVM were examined with the naked eye for visible particles whilst in their sealed boxes. On 7 of the 8 SBI small dark specs were observed on the PU-coating.
For exploratory purposes, 2 of the 10 Silimed PU-coated SBI used in the MSS were gently impressed with the adhesive side of Pritt transparent tape (Henkel AG & Co. KGaA, Germany). Examination of the adhesive side under a light microscope indicated the presence of a fibre that visually resembled the "glass fibres" described by TÜV SÜD and RMS. Analysis with scanning electron microscopy (SEM) coupled with electron dispersive X-ray spectroscopy (EDX) analysis identified this fibre as a man-made mineral fibre (MMMF) of the glasswool, rockwool, and slagwool family (Figures 1 and 2). The elemental composition was similar to the fibres reported by TÜV SÜD and RMS.

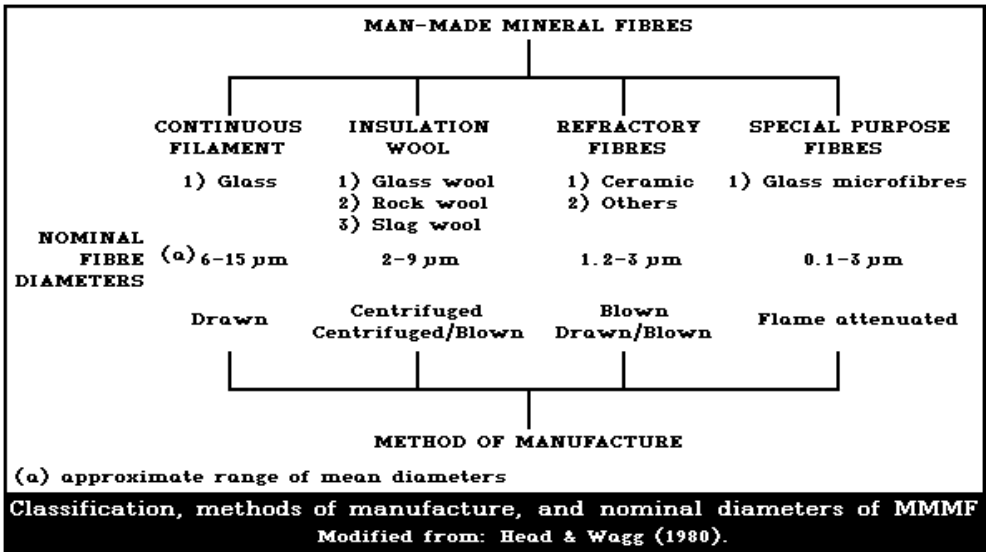

Figure 1. The family of mineral fibres as depicted in a WHO report on MMMF.[8]

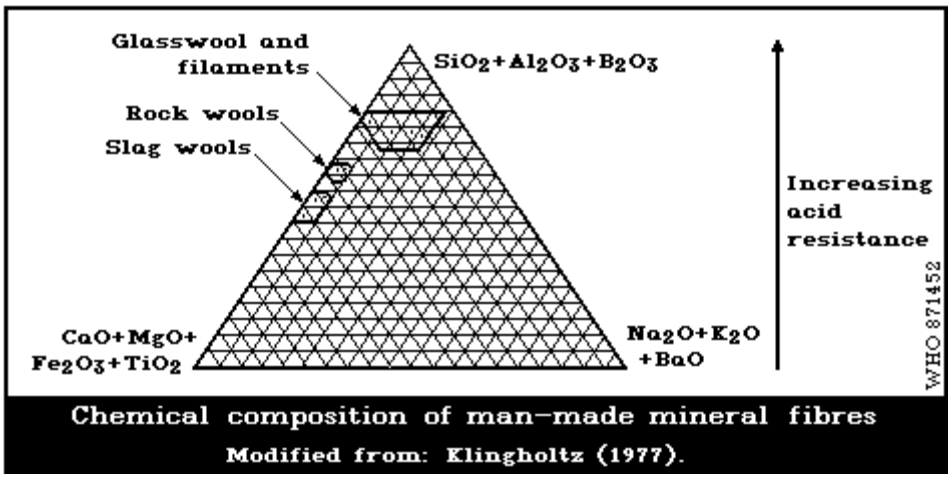

Figure 2. The chemical composition of certain mineral fibres as depicted in a WHO report on MMMF.[8]

This was the first indication these particles might also be present on Silimed PU-coated SBI. Because Silimed textured and PU-coated Silimed SBI were manufactured in the same building, this indicates a common source of contamination. For reasons of clarity the particles described by Silimed, TÜV SÜD and RMS as “glass fibres” will henceforth be addressed as MMMF.

2.4 Strategy for health risk analysis

Among the particles described in the TÜV SÜD and RMS reports, RIVM considered the MMMF as probably the most relevant for the risk analysis based on their expected hazardous properties (e.g. dimensions, composition, rigidity and biopersistence). Finding MMMF on Silimed PU-coated SBI was of particular relevance to the health risk analysis because: a) more women might be exposed to these fibres when they are on both Silimed textured and PU-coated SBI, and b) a more precise identification than ‘glass fibre’ would improve the health risk analysis. Although MMMF were also reported on a tissue expander, this health risk analysis is focused on SBI.

The strategy for the risk analysis was discussed in several telephone conferences with IGZ (NL) and European inspectorates. RIVM drafted a study proposal which was accepted by the agencies with a minor adjustment. The study was commissioned by the Medicines and Healthcare products Regulatory Agency (MHRA, United Kingdom), The Health Products Regulatory Agency (HPRA, Ireland), the Federal Agency for Medicines and Health Products (FAGG-AFMPS, Belgium), and IGZ. The study design is discussed in chapter 4.

3 Objectives

The primary objective of this study is:

1. To assess the health risks caused by particles found on Silimed SBI, MMMF in particular.

The related objectives of the laboratory investigations are:

2. To examine Silimed textured and PU-coated SBI and packaging for the presence of particles, MMMF in particular.
3. To determine the frequency of contamination of SBI with MMMF.
4. To determine the number of MMMF on the examined SBI and packaging.
5. To determine the dimensions and chemical composition of the MMMF on a representative number of SBI.

4 Investigational plan

4.1 Overall study design

The study consisted of a laboratory investigation and a risk analysis part. Risk analysis would primarily focus on the MMMF but could be adapted to laboratory findings, if necessary.
The laboratory investigation was primarily aimed at examining Silimed textured and PU-coated SBI for the presence of particles, MMMF in particular. The SBI in the study should ideally span a wide range of production dates, including production dates as early as possible. Three manufacturing periods were envisaged for sampling SBI (Fig. 1). SBI by other manufacturers were to be examined for comparison irrespective of their production dates.

The periods in Figure 3 were set considering two factors: a) a limited availability was expected for SBI manufactured before 2015 (especially prior to 2012), and b) the discontinuation of a drying tunnel implicated as a potential source of MMMF in the production of Silimed textured SBI in the end of June 2015. With respect to the drying tunnel, it should be noted that MMMF were still present on Silimed textured SBI after its discontinuation and that it was no part of the Silimed PU-coated SBI production line.[4, 9] This indicated a common source of MMMF. As the primary packaging of Silimed textured and PU-coated SBI appeared the same, these also needed to be examined for the presence of MMMF.

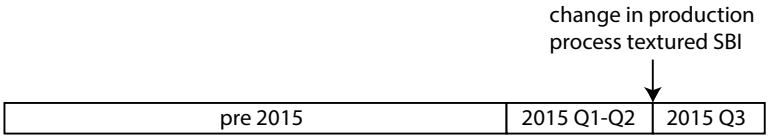

Figure 3. The three production periods envisaged to study.

4.2 Discussion of the study design

TÜV SÜD has reported the presence of MMMF on textured Silimed SBI manufactured in 2013, 2014 and 2015. TÜV SÜD also examined 4 Silimed PU-coated SBI manufactured in 2015 Q3 and reported finding no MMMF. However, exploratory experiments by RIVM indicate MMMF may also be present on Silimed PU-coated SBI manufactured in 2013. Among the particles described in the TÜV SÜD and RMS reports, RIVM considered the MMMF to be the most relevant for the risk analysis because of their dimension, composition and biopersistence. This includes the particles reported as ‘small straight fibres’ similar to the Silimed critical analysis ACR-116. The laboratory effort should thus be aimed at providing more information on all available SBI types regarding the identity and occurrence of MMMF and any new particles. Silimed smooth SBI were not available. This study does not take into account any of the other medical devices manufactured by Silimed (e.g. gluteal implants, tissue expanders).

As the SBI were not yet present at RIVM (except for 8 sealed Silimed PU-coated SBI) the risk analysis was started with the information

described in the TÜV SÜD and RMS reports. RIVM laboratory findings would serve as input to fine-tune risk analysis, if necessary.

4.3 Sampling plan for SBI

The Silimed SBI needed for this study comprised of textured and PU-coated Silimed SBI manufactured before 2015, in 2015 before the change in the production process, and SBI manufactured thereafter. It was envisaged to include 10 Silimed SBI from each type and each period (60 in total, see Figure 4). This number was chosen for practical reasons (availability, duration of the study). For comparison, 2 textured or PU-coated SBI from 3 other manufacturers were envisaged to be included (6 in total). For the comparator SBI no specific manufacturing dates were envisaged. As MMMF are persistent substances, SBI would be considered for inclusion even after the shelf-life had expired.

change in production process textured SBI

	pre 2015	2015 Q1-Q2	2015 Q3
texured	10	10	10
PU-coated	10	10	10

Figure 4. The samples per Silimed SBI type requested for this study.

Sealed Silimed SBI for the laboratory investigation would be provided by (or through) HPRA, MHRA, FAGG-AFMPS, and IGZ. Through HPRA, the Brazilian authority Anvisa was requested to sample unused packaging material at Silimed. As SBI would probably arrive gradually in the course of several weeks, it was planned to include and examine the first 10 of each type and period that were received. It was foreseen that not all of the envisaged samples might be obtained and examined within the time set for this study, which was the suspension period of the CE certificate.

4.4 Laboratory methods

For practical reasons a method described by TÜV SÜD was adopted, primarily aimed at finding MMMF. Alternative methods (e.g. vacuuming, liquid rinsing) were considered but required too much time to develop. The analytical method reported by TÜV SÜD used adhesive pads for a scanning electron microscope (SEM) in a laboratory environment. The sampled area (6 pads of about 5 cm^2 each) represented approximately 10-20% of the surface area of a 200-500 mL SBI. TÜV SÜD and RMS reports indicate that MMMF were not homogeneously distributed over the SBI surface area. Therefore, the number of MMMF found in the sampled areas may not be representative for the total number present on the entire SBI surface area. Further, it is unknown how effective particles are removed using SEM pads, nor whether MMMF remain intact in the removal process. Consequently, this method may result in underestimating (i.e. false negatives) or overestimating the actual number of particles. However, even the highest number of MMMF reported by TÜV SÜD was several orders of magnitude below the number of –much smaller– MMMF described in the toxicology studies that served as input for the health risk analysis.[3, 10]

All included SBI were examined by light microscopy. During sampling, control SEM pads with the adhesive side exposed to the air were placed on the laboratory bench to obtain background information on particles from the laboratory air. For each set of 10 SBI included in the study, at least 4 SBI were forwarded to SEM microscopy, depending on the number of samples received and light microscopy findings. SEM coupled with energy dispersive X-ray spectroscopy (EDX) was used to confirm the presence of MMMF and investigate the elemental composition of other particles.

4.5 Risk analysis

The scope of the risk analysis was to determine the human health risk of the MMMF that have been found on the surface of breast implants. The risk analysis started with the identification of the fibres, based on their dimensions, rigidity and composition as reported by TÜV SÜD and RMS (section 5.1). This was followed by an exposure assessment. Subsequently, the hazardous properties including an eventual dose response relationship of MMMF are explored, with a focus on the factors that are relevant for the fibres at hand. The actual risk analysis is presented in 5.8.

5 Laboratory findings

5.1 Samples provided

5.1.1 *Silimed SBI*

A total of 66 Silimed SBI were received from IGZ (8 PU-coated SBI), MHRA (13 PU-coated, 20 textured), HPRA (1 PU-coated SBI, 9 textured SBI), Infarmed, Portugal (10 textured SBI), and through the Central Authority of the Länder for Health Protection with regard to Medicinal Products and Medical Devices (ZLG), Germany (5 textured).
The eldest SBI was manufactured in 2009. See Table 1 and see Appendix 1 for details. Silimed PU-coated SBI manufactured in 2015 Q3 were not among the received SBI. Unused Silimed primary packaging material was not received either.

Examination of the packaging showed that Silimed SBI manufactured before May 2014 were labelled “CE0197”, corresponding with the previous notified body TÜV Rheinland. Silimed SBI manufactured after May 2014 were labelled “CE0123”, corresponding with the current notified body TÜV SÜD. TÜV SÜD indicated in an e-mail that their CE certificate for Silimed was issued on March 11th, 2014.

5.1.2 *Comparator SBI*

Sealed comparator SBI were received from MHRA (12x Brand A), IGZ (4x Brand C), and CyMDA, Cyprus (5x Brand B).

5.2 Inclusion

Table 1 shows the target number of SBI for inclusion, the number of SBI received and the number of SBI included (see also Figure 5). Deviations from the target number were caused by the gradual influx of SBI and lack of availability. For Silimed PU-coated SBI, 11 samples were included because a later shipment contained the first SBI manufactured in 2009-2012. For Brand A, 4 SBI were included rather than 2 because it was uncertain whether other comparator SBI would be available. When they did arrive it was decided to include 4 of these comparators as well. Eventually, 39 Silimed SBI were included and 12 comparator SBI. Not included were 5 Silimed textured SBI manufactured in 2015 Q1-Q2 that were received after the laboratory examinations had been finalised.

Table 1. The target number of SBI, and the number received and included.

manufacturer	type	target	received	included
Silimed Pre 2015	PU-coated	10	22	11
	Textured	10	21	10
Silimed 2015 Q1-Q2	PU-coated	10	8	8
	Textured	10	11	6
Silimed 2015 Q3	PU-coated	10	0	0
	Textured	10	4	4
Brand A	Textured	2	15	4
Brand B	PU-coated	2	4	4
Brand C	Textured	2	5	4

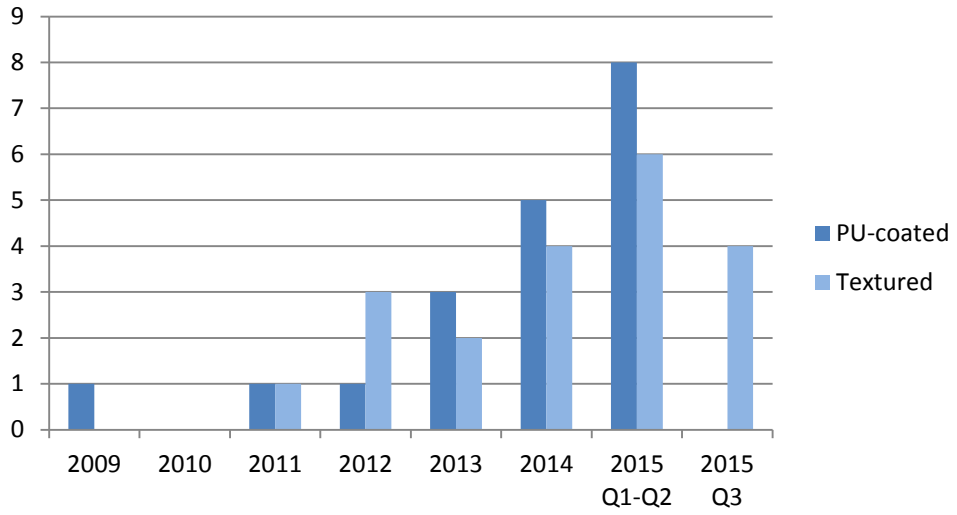

Figure 5. Number of Silimed SBI included in this study per year of manufacturing.

5.3 Results for Silimed

5.3.1 MMMF on Silimed PU-coated SBI

In the first series analysed, all 8 Silimed PU-coated SBI were positive for the presence of MMMF. Essentially, two different types of MMMF were observed. Most of the MMMF (type 1) showed an elemental composition high in Si, Ca, O, and Al; approximately 15.2 % Al_2O_3, and low in Mg, K and Na; approximately 0.9% Na_2O. Some of the MMMF (type 2) were high in Na; approximately 16.6 % Na_2O and low in Al; approximately 4.7 % Al_2O_3. The dimensions of MMMF type 1 and 2 largely overlapped. Together they had an average diameter of 9 ± 2 µm (range 1.4–10.7 µm and an average length of 115 ± 92 µm (range 20–387 µm). The average amount of MMMF was 6 ± 4 per 6 pads used per implant (range 0–14). The surface of a pad is 5 cm^2 and the surface of a 500 mL hemisphere is 362 cm^2. If the MMMF are homogeneously distributed over the surface of the implant, an average of 71 MMMF are found on a large size implant. This number of MMMF is similar to the amount of MMMF on Silimed textured SBI reported by TÜV SÜD and RMS.

Screening of the packaging inside yielded 1 MMMF indicating that the MMMF preferred to adhere to the PU-coated SBI. Therefore, examination of the packaging was no longer pursued.

In the second series, 11 more Silimed PU-coated SBI were analysed for particles and specifically for MMMF. Particles were observed at the surface of all of the SBI examined. MMMF were observed on 5 SBI and organic fibres were observed on all.

Overall, 13 of the 19 Silimed PU-coated SBI examined were positive for MMMF, see Figure 6. No MMMF were observed at the sampled areas of 6 SBI. The SBI production dates of the implants ranged from 2009 to the first half of 2015, see Figure 5.

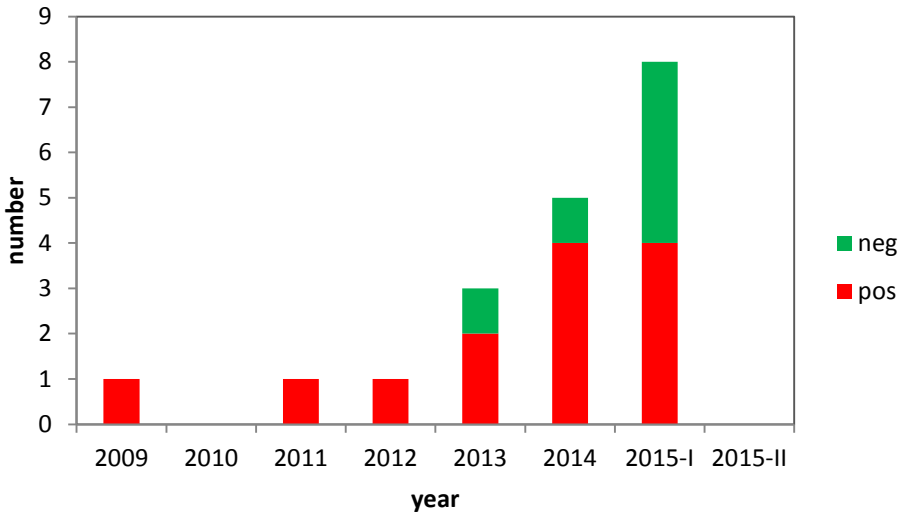

Figure 6. The examined PU-coated Silimed implants per year of production. The numbers of implants found positive for man-made mineral fibres (MMMF) are highlighted in red; the numbers negative for MMMF are highlighted in green.

5.3.2 *Non-MMMF particles on Silimed PU-coated SBI*

In the first series of Silimed PU-coated SBI analysed, all 8 SBI were positive for the presence of non-MMMF particles on their surfaces. In all cases organic fibres were observed, spherical glass-like particles, silicium/carbon-rich particles, iron/chromium/nickel-rich particles and silicium/oxygen-rich particles. In some cases other particles were detected that were rich in iron, silver, or copper.
The spherical glass-like particles had an average size of 50 ± 23 µm (range 20–100 µm). The silicium/carbon-rich particle displayed an elemental composition and shape similar to that of granular siliciumcarbide. See Appendix 2 for exemplary SEM-EDX images.
Appendix 2 also shows the SEM-EDX images for one of the dark specs observed in the exploratory assessment. This particle was cut out of the SBI surface with some of the surrounding PU-coating. The SEM-EDX images showed an iron-rich particle which appears to be fused to the PU-material. The iron/chromium/nickel-rich particles were tentatively identified as metal alloy scrapings.
The range of foreign particles that were detected during testing may suggest more than one single source of contamination. Most of the non-MMMF particles found by RIVM were not reported earlier as particulate contamination on Silimed SBI. Although there is no rationale for the presence for any of these foreign particles on the SBI surface, the project team decided (based on the available data) that MMMF remained the most important particles for the risk analysis.

5.3.3 *MMMF on Silimed textured SBI*

A total of 20 Silimed textured SBI were analysed for the presence of particles. The SBI production dates ranged from 2011 to the third quarter of 2015, see Figure 7. In all cases, particles were observed (e.g. organic fibres). Overall, 10 of the examined Silimed textured SBI were positive for MMMF. The 4 Silimed textured SBI examined produced after June 2015 were negative for MMMF. Since TÜV SÜD reported MMMF on all of their 4 Silimed textured SBI produced after June 2015 we conclude

that sample size and non-random distribution may contribute to a negative screening result.

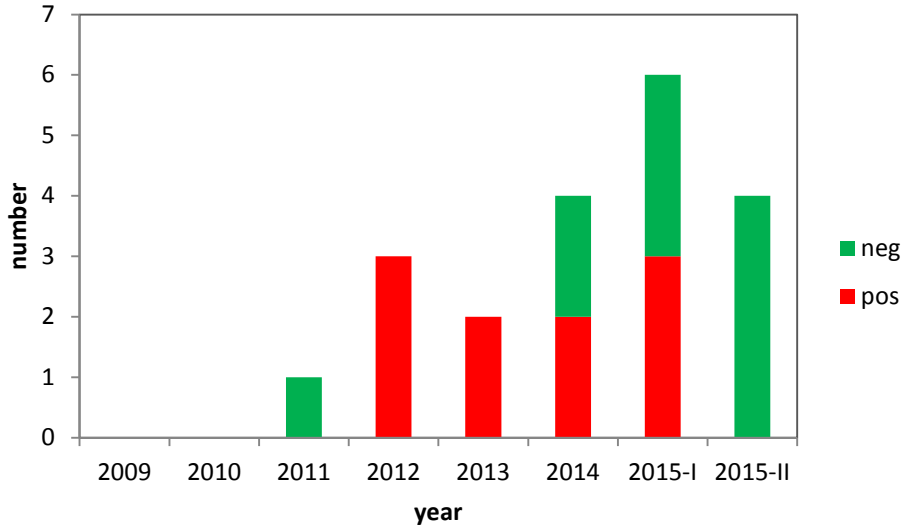

Figure 7. The examined textured Silimed implants per year of production. The numbers of implants found positive for man-made mineral fibres (MMMF) are highlighted in red; the numbers negative for MMMF are highlighted in green.

5.3.4 Non-MMMF particles on Silimed textured SBI

On the surface of the Silimed textured SBI some organic fibres were observed similar to those reported by TÜV SÜD and RMS. No other non-MMMF particles were observed.

5.4 Results for comparator SBI

The comparator SBI were investigated for the presence of particles, specifically MMMF. Some particles were found at the surface of all comparator SBI examined (e.g. organic fibres).
MMMF were not observed on the examined SBI from Brand A and B. However, MMMF were observed on 2 of the 4 examined SBI of Brand C. These MMMF showed an elemental composition different from the fibres found on the Silimed implants (hence a MMMF type 3). Especially the Mg (9.6 % MgO) and Fe (6.9 % Fe_2O_3) content were higher based on a semi quantative analysis of the EDX data. The average diameter was 4 ± 2 µm (range 1.4 - 7.8 µm) and the average length was 223 ± 161 µm (range 61 - 514 µm). Clusters of fibres of varying size were found (see Appendix 2). The range of MMMF on the SEM pads was 2 - 7, which is similar to Silimed SBI. On one of the Brand C SBI examined a fluoro-rich particle was observed which was tentatively identified as Teflon.

5.5 Laboratory input for the risk analysis on MMMF

The laboratory investigation showed that both Silimed textured and PU-coated SBI might have been contaminated with MMMF, at least since 2009. The identity, dimensions and number of MMMF found in this study are similar to the those reported by TÜV SÜD and RMS. MMMF were not detected on the control SEM pads exposed to the air. This justifies the initial approach for the risk analysis. Additional studies are required for the comparator SBI.

6 Risk analysis

6.1 Identity of the fibres

6.1.1 *Measurement data of the MMMF on the implants*

Samples of Silimed implants were analysed in two studies. The first study (report date: 09-07-2015) was performed by RMS in Switzerland. The second study (report date: 28-07-2015) by TUV SUD in Germany. The results concerning the MMMF are shortly summarized.

Study 1:
In the first study, nine implants with textured surfaces and nine tissue expanders, all produced in the period 2013-2015, were analysed. The optical and stereo microscopy assessment of the sample surface at 50-fold magnification revealed the presence of particles, organic fibres or MMMF on all investigated samples. The MMMF were clearly identified by electron optical and EDX analysis. To this end, the particles were removed from six patches per implant with adhesive carbon tape pads of about 25 mm in diameter (Figure 8).

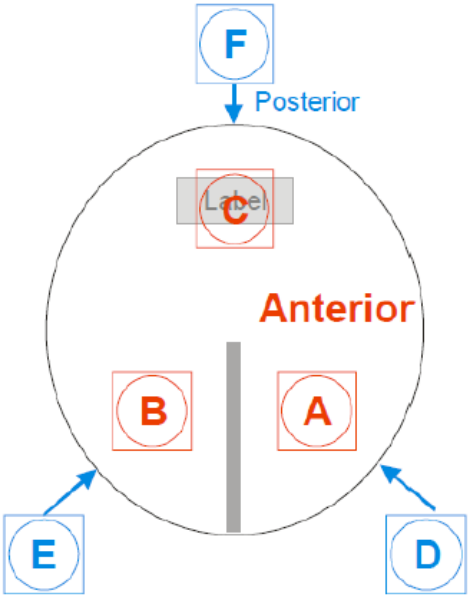

Figure 8. Indication of the approximate positions of the carbon tape-pads placement for removing the residues from the surface (D, E, and F are identical positions to A, B, and C, but on the posterior side of the implant).[3]

MMMF were found on 9/9 breast implants while only 1/9 tissue expander showed MMMF. It must be noted that the MMMF are not homogenously distributed over the surface. One example was given of an implant with 12 fibres at one patch location and 2 fibres each on four other locations. The mean diameter of the MMMF was found to be 8-10 µm. Most particles were between 100 and 300 µm long, with outliers of more than 1000 µm (Figure 9). The results of the EDX mapping of the fibres can be found in Table 2. Particles were found on all samples in various

amounts. Increasing the magnification dramatically increased the number of clearly identified particles [1].

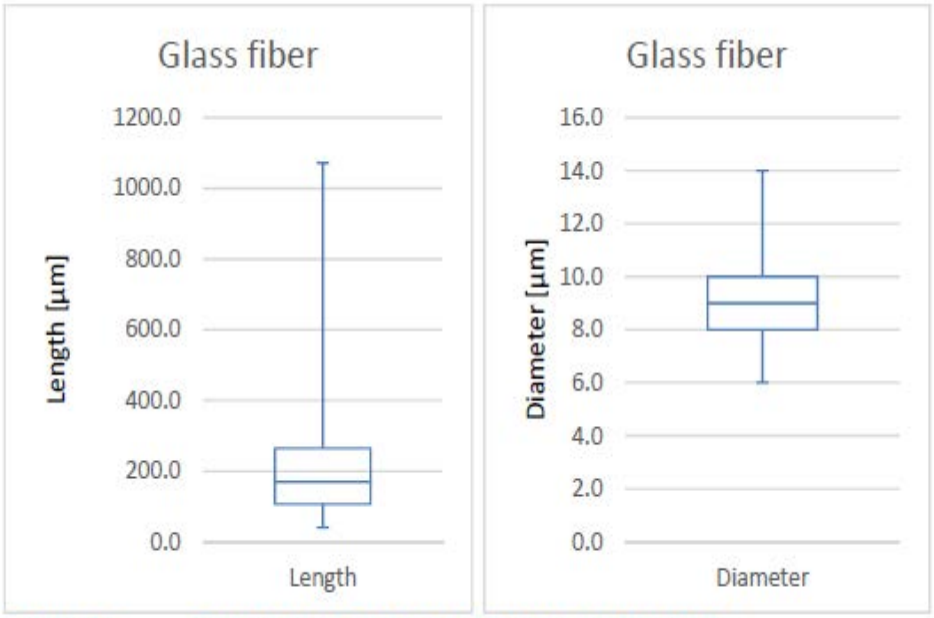

Figure 9. Box plot of all glass fibre found upon analysis.[1]

Table 2: Chemical composition of fibres in percentages [1]

SAMPLES	C	O	F	Na	Mg	Al	Si	K	Ca	Ti	Fe	P	S
Median		44.1	0.2	0.3	0.3	8.2	28.2	0.4	16.1	0.2	0.2	0.0	0.0
min		34.0	0.0	0.0	0.1	7.6	24.6	0.0	0.0	0.0	0.0	0.0	0.0
max		52.0	4.2	0.7	0.9	8.9	31.0	20.7	26.2	0.6	0.3	0.0	23.2

Study 2:
In the second study, twelve SBI were analysed: 4 smooth, 4 textured and 4 PU-coated. All twelve implants were produced after a potential source of fibres, a drying tunnel used after final cleaning, was shut down at the 16th of June 2015.
The same adhesive pads were used as in the RMS study to collect samples, with again six pads per implant. MMMF were quantified using the stereo microscope, covering the whole surface of the sample pads. The MMMF were clearly recognizable with the stereo microscope at 2-fold magnification.
No MMMF were found on implants with polyurethane surface and smooth surface, but MMMF were found on all four implants with textured surface. The total number of fibres at the surface of the pads (1 pad = 4,909 cm², 6 pads = 29,454 cm²) detected was 6, 1, 3, and 3 per implant. The chemical composition matched with study 1. Also, small fragments of fibres were observed (not counted as MMMF, because they were not clearly recognizable with the stereo microscope).
In addition, all particles were counted at 100-fold magnification on 10 spots of 5 mm^2 per pad. Several forms of particles were found, including organic fibres and a single silver particle. The average number of

particles per cm^2 is given in Table 3 (below). It is unclear whether or not the small straight fibres also include MMMF, as the chemical composition of these particles was not determined.

Table 3: Particle counts in number of particles per cm^2 (sum of particle counts per 6 pads). Please note that the discrimination between type B particles (irregular shaped) and type D particles (rounder particles) was hardly possible at 100-fold magnification and therefore all particles were counted as type B particles. Note: the first value for 'Fibres straight per cm^2' should be 3 instead of 1. [3]

Sample	Fibers curled per cm²	Fibers straight per cm²	Particles > 20 µm per cm²	Particles < 20 µm per cm²	Textile fibers per cm²
1 textured	3	1	26	120	1,1
2 textured	1	2	28	156	1,2
3 textured	2	3	18	144	2,4
4 textured	2	4	115	279	2,1
5 polyurethane	3	4	17	160	2,4
6 polyurethane	3	2	22	90	2,0
7 polyurethane	2	1	12	123	1,6
8 polyurethane	2	2	7	55	1,3
9 smooth	1	1	5	42	0,4
10 smooth	0	2	10	56	0,8
11 smooth	1	1	5	50	0,6
12 smooth	1	2	3	36	1,0
Blank	0	0	0	1,7	0,2
Settling plate	0	0	0,2	0	0,6

6.1.2 *Comparison with other man-made mineral fibres*

There are various forms of MMMF, which differ in size, chemical composition, solubility and biodegradability, see Figures 1 and 2. According to monograph 43 of IARC (International Agency for Research on Cancer), Man-made mineral fibres is a generic term that denotes fibrous inorganic substances made primarily from rock, clay, slag or glass. These fibres can be classified into three general groups: glass fibres (comprising glasswool and glass filament), rockwool and slagwool, and ceramic fibres.

Compared to these three groups, the composition of the MMMF found on the implants has the closest match with Rockwool and slagwool (see Table 4 and Table 5). Rockwool is typically made from igneous rocks such as diabase, basalt and olivine, and carbonate rocks containing 40-60% calcium and magnesium carbonates. Slagwool is made from the fused agglomerate by-products of certain metal smelting processes and its exact composition varies depending on the source of the starting material. The absence of significant amounts of sodium and boron is typical of slagwool; it is essentially a calcium aluminium silicate with varying amounts of magnesium and iron, and is usually slightly soluble in hydrochloric acid.

Table 4: Chemical composition of mineral wools. [11]

	Continuous glass filament[a]	Glass wool[b,c] Insulation wool	Glass wool[b,c] Special-purpose fibre	Rock (stone) wool[d]	Slag wool[b,c]	Refractory ceramic fibres[e]	Alkaline earth silicate wool[e]	High-ahnnina, low-silica wool[f]
SiO_2	52–75	55–70	54–69	43–50	38–52	47–54	50–82	33–43
Al_2O_3	0–30	0–7	3–15	6–15	5–16	35–51	<2	18–24
CaO	0–25	5–13	0–21	10–25	20–43	<1		
MgO	0–10	0–5	0–4.5	6–16	4–14	<1		
MgO + CaO	0–35	5–18	0–25.5	16–41	24–57		18–43	23–33
BaO	0–1	0–3	0–5.5					
ZnO	0–5		0–4.5					
Na_2O		13–18	0–16	1–3.5	0–1	<1		
K_2O		0–2.5	0–15	0.5–2	0.3–2	<1		
$Na_2O + K_2O$	0–21	12–20.5			0.3–3		<1	1–10
B_2O_3	0–24	0–12	4–11	<1	<1		<1	
Fe_2O_3[g]	0–5	0–5	0–0.4		0–5	0–1	<1	
FeO				3–8				3–9
TiO_2	0–12	0–0.5	0–8	0.5–3.5	0.3–1	0–2		0.5–3
ZrO_2	0–18		0–4			0–17	0–6	
$Al_2O_3 + TiO_2 + ZrO_2$							<6	
P_2O_5				<1	0–0.5			
F_2	0–5	0–1.5	0–2					
S					0–2			
SO_3		0–0.5						
Li_2O	0–1.5	0–0.5						

Table 5: Chemical composition of different types of rockwool and slagwool. [12]

Component	Rockwool[a] 1	Rockwool[a] 2	Rockwool[a] 3	Slagwool[a] 1	Slagwool[a] 2
SiO_2	52.92	47.5	45.54	41.0	40.58
Al_2O_3	6.52	13.0	13.38	11.8	12.52
MgO	–	–	–	–	–
CaO	30.28	16.0	10.80	40.0	37.50
FeO	1.01	7.0	5.75	0.9	1.0
TiO_2	0.51	1.5	1.99	0.4	0.44
MnO	0.06	0.5	0.24	0.6	0.30
Na_2O	2.29	2.5	2.52	0.2	1.45
K_2O	1.57	1.0	1.36	0.4	0.30
SO_3	–	–	–	–	–
P_2O_5	0.15	–	0.06	0.3	0.21
Fe_2O_3	1.48	0.5	8.22	–	–
CaS	–	–	–	–	1.04
S	–	–	–	0.4	0.46
F[c]	–	–	–	0.4	–

[a]From Mansmann *et al.* (1976)

Compared to the chemical composition of rockwool and slagwool, the fibres on the implants have the high Si, O, Al, Ca and low Na, K, and Ti content in common with both materials. The presence of Fe is more typical for rockwool, but low amounts have also been detected in slagwool. So, the low Fe concentrations found in the samples do not allow making a distinction. Generally, rockwool and slagwool have higher Mg contents than found in the fibres, but as can be seen in Table

5 some also do not contain Mg. Hence, the concentration of Mg varies too much to be determinative. It should be mentioned that the fibres on the implants show a high variation in some elements (F, K, Ca, S). Thus, it cannot be excluded that some of these fibres are of a different type.

6.1.3 Conclusion fibre identity

Due to the variable composition of fibres and mineral wool, it is difficult to determine the exact identity of the fibres on the breast implants. The closest similarity is to rock- and slagwool, but other types of fibres might also be present.

6.2 Exposure assessment

The number of MMMF per implant is calculated by extrapolation of the numbers found on the adhesive pads to the total surface area of the implants.

To calculate the surface area of the breast implants, it is assumed that they have a maximum volume of 500 mL and have the shape of a hemisphere.

The volume of a sphere is given by the formula $V = (4/3)\pi r^3$. For a spherical shaped volume of 1 L, the radius r would be $(3/4/\pi)^{1/3} = 0.62$ dm. The radius can be used to calculate the surface area of a hemisphere, as displayed in Figure 10.

Following from this the surface area of a breast implant (half a sphere + a circle) is:
Surface area of half a sphere: $1/2 \times 4\pi r^2 = <r = 0.62 \text{ dm}> = 2.4 \text{ dm}^2$
Surface area of flat side of the sphere: $\pi r^2 = 1.2 \text{ dm}^2$
Total surface area implant: $2.4 + 1.2 = 3.6 \text{ dm}^2 =$ **362 cm²**

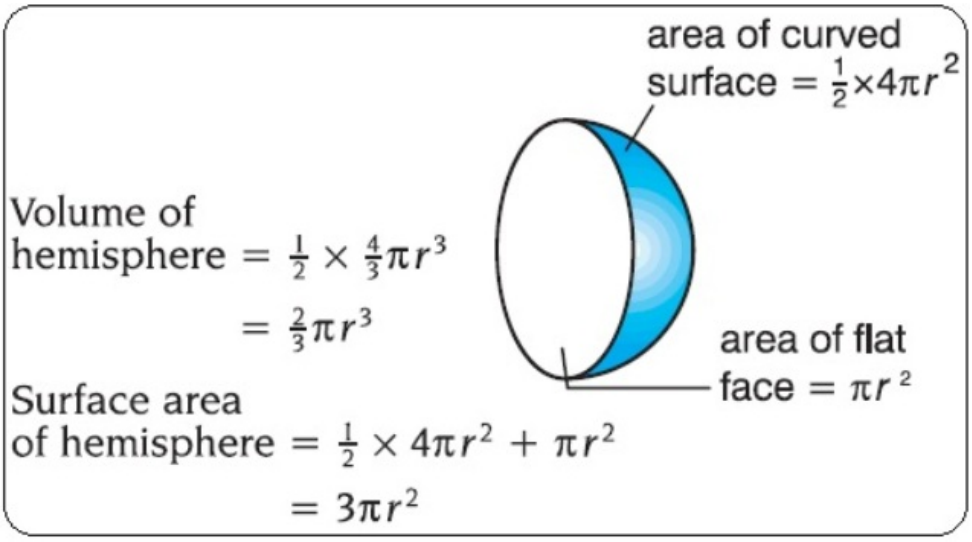

Figure 10. Calculation of the surface area of a hemisphere [13]

In the study by TÜV SÜD, MMMF were found on all four implants with textured surfaces. The total number of glass fibres at the surface area of the pads (1 pad = 4,909 cm², 6 pads = 29,454 cm²) detected with 2 fold magnification was 6, 1, 3, and 3 per implant.

Assuming that the samples are representative for the fibre distribution on the total surface of the implants, the highest number of fibres per implant is 73.

The TÜV SÜD report states that it counted fibres as MMMFs when recognisable under a stereo microscope at 2x magnification. It also mentions that *"… small fragments of glass fibres were observed (not counted as glass fibre as shown in Table 3 because they were not clearly recognizable with the stereo microscope)".*[3] This means that there are actually more MMMF present than accounted for in their Table 3. Small straight fibres were mentioned in the results of a particle count at 100x magnification. Upon our e-mailed question whether the small glass fibre fragments were counted among the 'small straight fibres', TÜV SÜD replied that they had not identified the 'small straight fibres'. Yet both Silimed and Exponent treat these particles as MMMF in their risk analysis. For that reason we present two scenario's for the risk analysis, one scenario counting only the long MMMF and a second scenario including the 'small straight fibres' as MMMF fragments >20 µm. The highest density of these fibres was 4 per cm^2, which corresponds with 1440 fibres/implant.

Assuming exposure from two textured implants, the total maximum exposure of one person would be (73+1440)*2 = 3026 or $3*10^3$ fibres.

6.3 Hazard assessment

In this part of the assessment, the available, relevant information on the hazard of MMMF will be considered, with a focus on carcinogenicity. It is important to note that virtually all experimental and epidemiological studies on fibre toxicology looked at adverse effects of inhalable fibres on the lungs and pleura. Unfortunately, no studies were identified that investigated fibres of similar (non-inhalable) size as have been found on the breast implants, nor studies using chronic intra-muscular/intra-mammary exposure.
In this chapter, the available information on inhalable fibres will be combined with the general factors that determine the toxicity of fibres to gain an estimation of the potential toxicity of the fibres found on the breast implants.

6.4 The fibre toxicity paradigm

In respiratory toxicology, it is generally accepted that high aspect ratio particles (fibres) pose an additional hazard beyond that produced by conventional compact particles. A high aspect ratio is defined by the WHO as a ratio of fibre length to diameter ≥3 (WHO 1988). The toxic potential of fibres is often described with the 3Ds of particle toxicology: Dose, Dimension, and Durability (Bernstein DM 2007). The mechanism of these factors and their contribution to the toxicity of fibres after implantation will be shortly discussed.

- The dose usually refers to the number of long fibres that reach the lung parenchyma and cannot be removed by macrophages or by other clearance mechanisms of the lungs. In case of implantation, the dose is the total number of fibres on the breast implant.

- The dimension refers to the length and diameter of the fibres. The dimension influences both the uptake of the fibres through inhalation and the durability in the body. The influence of the diameter on the uptake is specifically relevant to inhalation, as fibres with a diameter over 3 µm cannot be inhaled into the deep lung. This is not applicable to implantation. The length determines whether the fibre can be engulfed and removed by the macrophage (see Figure 11), which applies regardless of the route of exposure.

- The durability determines how fast the fibre can dissolve and/or break down once deposited in the lung. The durability depends on the dimension and composition of the fibres and the characteristics of the local environment. Durability is a contributing factor regardless of the route of exposure; however the local environment can differ in different parts of the body. Thus, there may be a difference in durability between inhaled and implanted fibres.

An overview of the relationship between fibre characteristics and their (inhalation) pathogenicity is described by a structure : activity paradigm, displayed in Figure 11.[14]

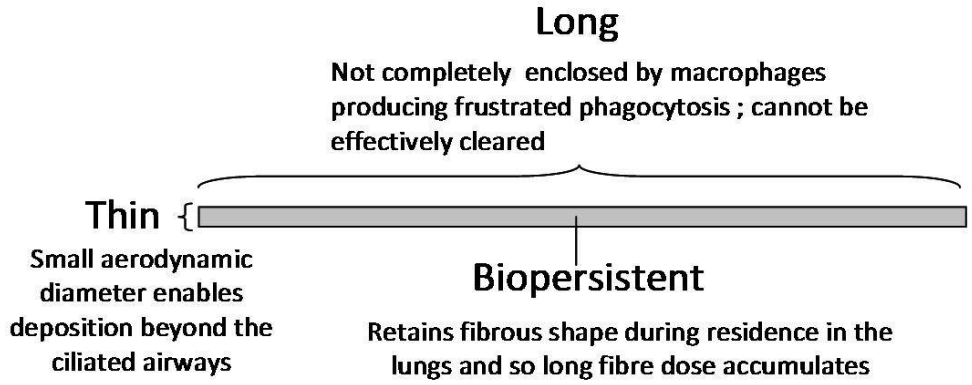

Figure 11. The fibre paradigm. [14]

When long, thin, biopersistent fibres enter the body they cannot be cleared by macrophages or by other clearance mechanisms. Hence they accumulate and cause chronic inflammation reactions, which lead in time to the formation of fibrosis and granuloma. Although this mechanism was first described for asbestos, it occurs irrespective of the chemical composition of the fibres, as long as they are biopersistent and of the right shape. In Figure 12, the mechanism of frustrated phagocytosis is visualized for both asbestos and carbon nanotubes.

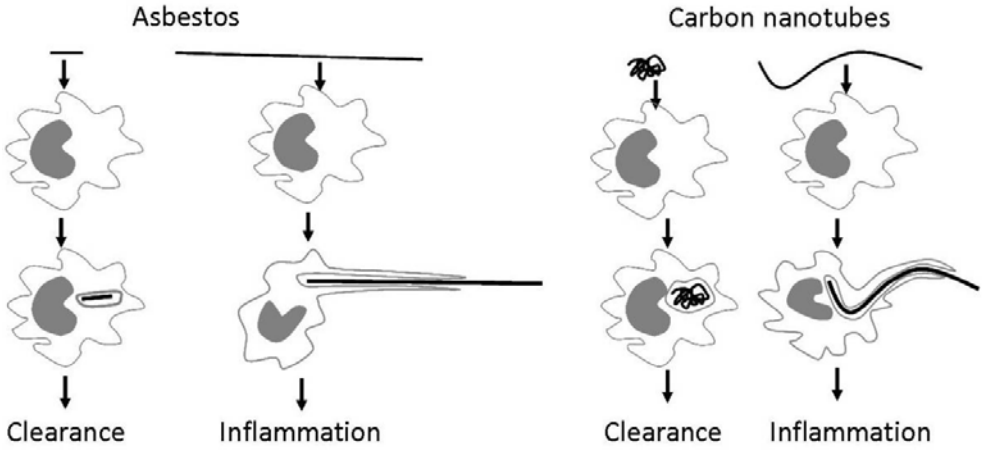

Figure 12. The frustrated phagocytosis paradigm as it relates to long and short fibres as asbestos (left) and various forms of carbon nanotubes (right) [14]

6.5 Evaluation of fibre characteristics and their relation to toxicity

It should be noted that the long mineral fibres identified on Silimed breast implants are too large to be inhaled. As these cannot be inhaled no hazard studies have been performed using fibres of these dimensions. To fill this gap, information has been collected on MMMF, with an emphasis on rock and/or slagwool, which are most relevant to the toxicity of the fibres of interest. This includes more detailed information on the influence of the dimensions, rigidity, and biopersistence of the fibres on their toxicity.

In a study by Miller et al., a range of respirable MMMF were tested for carcinogenicity in rats after intraperitoneal injection.[10] An overview of the fibres tested and their length distribution is given in Table 6. The persistence of the fibres is given in Table 7, measured both as the dissolution in vitro in sodium oxalate and as persistence in the lung 12 months after intratracheal administration. The resulting tumour incidences and survival time are given in Table 8.

The results of this study show a difference in carcinogenic potential between stone wool and slagwool, with a 95% incidence of mesothelioma in the rat peritoneal cavity for rockwool versus a 54% incidence for slagwool. Attempts were made by the authors of the study, using regression models, to relate these differences in toxicity to fibre dimensions and to measures of durability from separate experiments. The results pointed principally to a link with the injected numbers of fibres >20 µm in length and with biopersistence in the rat lung of fibres longer than 5 µm.[10]
This relation between long, persistent fibres and tumour incidence was seen for both the mineral fibres (glass-, stone-, slagwool) and for the refractory ceramic fibres (RCFs).

When considering the principle of fibre tumorigenesis, the critical fibre size depends amongst others on the size of the macrophages. According to Krombach et al., the coulter counter tests showed a diameter of 13.1 and 13.5 µm for rat and hamster alveolar macrophages and for human alveolar macrophages a diameter of 21.2 µm was

determined.[15] This may explain the finding that fibres >20 µm are more toxic than shorter fibres.

Table 6: Distribution of injected fibre dose in two diameter classes and six cumulative length classes [10]

Fibre label	Fibre type	Mass dose (mg)	Diameter class	Numbers of injected fibres ($\times 10^6$)					
				Length category (μm)					
				>0.4	>5	>8	>10	>15	>20
100/475	Glass microfibre	8.3	<0.95 μm	11034	1868	680	421	186	9
			>0.95 μm	12	12	12	12	0	0
SiC 1	Silicon carbide whisker	14.2	<0.95 μm	821	577	387	307	185	121
			>0.95 μm	4	3	3	3	3	1
Amosite	Amosite asbestos (long-fibre)	6.1	<0.95 μm	1791	402	225	164	103	63
			>0.95 μm	10	8	8	8	8	8
MMVF 10	Glass wool	144.4	<0.95 μm	376	314	264	236	155	119
			>0.95 μm	665	659	598	567	506	436
MMVF 21	Stonewool	183.1	<0.95 μm	1349	1012	744	628	439	344
			>0.95 μm	701	644	558	514	411	335
MMVF 22	Slagwool	129.6	<0.95 μm	898	671	492	402	263	142
			>0.95 μm	570	544	466	388	291	207
RCF 1	Refractory ceramic fibre	110.9	<0.95 μm	713	394	280	228	129	85
			>0.95 μm	398	374	302	260	194	140
RCF 2	Refractory ceramic fibre	188.8	<0.95 μm	958	619	392	320	201	111
			>0.95 μm	565	550	480	455	340	231
RCF 4	Heat-treated RCF 1	90.4	<0.95 μm	648	264	134	81	15	6
			>0.95 μm	548	466	311	230	111	36

Table 7: Measures of fibre durability: in vitro dissolution in sodium oxalate at pH 7.0 over 56 days; and persistence in the lung over twelve months after intratracheal injection, in selected cumulative length classes.[10]

Fibre label	k_{dis} (ng.cm^{-2}.hr^{-1})	Adjusted k_{dis} (mg.g^{-1}.hr^{-1})	Persistence (%) of injected fibres at 12 months					
			Length category (μm)					
			>0.4	>5	>8	>10	>15	>20
100/475	9.1	0.466	9.9	21.3	22.9	29.6	17.2	23.7
SiC 1	0.2*	0.002*	52.6	53.7	47.7	49.2	54.5	59.2
Amosite	0.2*	0.002*	8.9	21.9	29.4	34.4	46.2	68.8
MMVF 10	122.4	1.310	13.1	9.4	6.0	4.4	2.1	0.6
MMVF 21	28.9	0.399	36.9	37.8	37.7	36.3	36.6	43.0
MMVF 22	52.8	0.602	16.6	10.6	6.1	3.8	2.2	1.7
RCF 1	4.4	0.064	40.3	42.8	44.9	46.6	49.6	50.5
RCF 2	3.1	0.035	59.1	70.8	83.9	99.9	130.0	157.3
RCF 4	0.5	0.005	72.2	81.2	95.7	108.4	113.1	142.7

Table 8: Summary of mortality experience for each fibre type.[10]

Fibre label	Animals in group	Number with mesothelioma	%	Median all-cause survival (days)	*Estimated standard error*	Median mesothelioma survival (days)	*Estimated standard error*
100/475	24	8	*33*	642	*	679	*24*
SiC 1	24	22	*92*	250	*45*	257	*52*
Amosite	24	21	*88*	509	*27*	509	*27*
MMVF 10	22	13	*59*	643	*87*	676	*43*
MMVF 21	20	19	*95*	281	*	284	*
MMVF 22	24	13	*54*	658	*	695	*
RCF 1	24	21	*88*	337	*17*	337	*17*
RCF 2	18	13	*72*	376	*25*	391	*25*
RCF 4	22	0	*0*	725	*	†	†

* Sparse data—no reliable estimate.
† No deaths—function not defined.

The question that arises from the study by Miller et al. is what makes stone wool fibres (MMVF 21) more persistent than glasswool (MMVF 10) and slagwool (MMVF 22).

The relation between chemical composition and biopersistence has been described in a review by Bernstein.[16] A summary of the influence of the chemical composition on the biosolubility of fibres is given in Figure 13. This shows the influence of a chemical component in the fibre on the decrease or increase in dissolution rate (K_{dis}). The coefficient is derived from experimental data by Eastes et al.[17] A negative coefficient, means that increasing amounts of this component decreases the dissolution rate (biosolubility) in borosilicate glass compositions. Most cations increase the biosolubility of the fibres (thus decrease the persistence), while silica and aluminium decrease the solubility and increase their persistence.

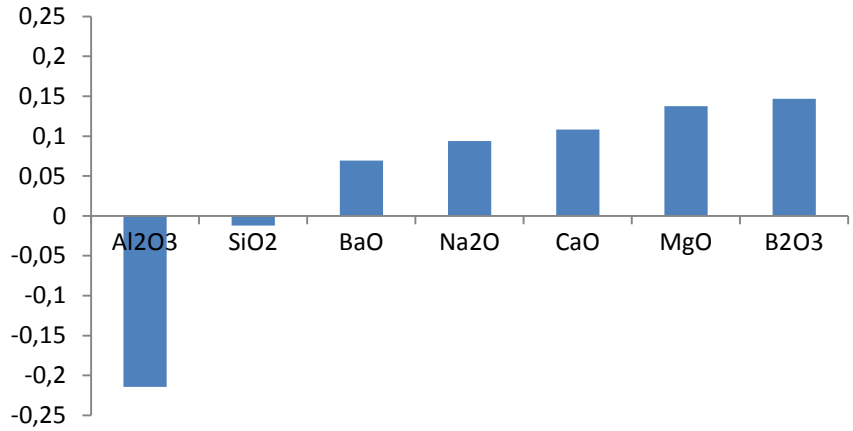

Figure 13. The influence of chemical components on fibre biosolubility. The figure is reproduced from Eastes et al. [17]

As can be seen in Table 4, both stone and slagwool vary in their composition, which is reflected by the wide variation in persistence also within each group, as illustrated by Table 9. Unfortunately, the chemical composition of the rockwool and slagwool types MMVF 21 and MMVF 22 tested in the 1999 Miller et al study, could not be found. Without this knowledge, no conclusion can be drawn on the relation between the composition of the fibres and their persistence and toxicity.

Under the EU regulation on Classification, Labelling and Packaging (CLP), the effect of composition on the biopersistence and carcinogenic potential has led to a division of MMVFs in two categories with different classifications for carcinogenicity (Table 10).[18] The fibres with a total of alkaline oxides and earth alkalis greater than 18% are placed in Category 2 (suspected human carcinogen), while those with less than 18% are classified as Category 1B carcinogen (presumed human carcinogen). A more detailed analysis of rationale behind the classification of MMMF is given by Bernstein (2007).[16]
As can be seen from Table 2, the fibres on the implants have a total median Na, K, Ca, Mg content of 17% (Ba was not determined). When the percentage of Ca (16.1%) is corrected for the oxide, the content of CaO alone is already 22.5%. This indicates that most of these fibres belong to the mineral wools, which are classified as Category 2 carcinogens.

Table 9: Clearance half-time of mineral fibres as determined by the inhalation biopersistence protocol [16]

Fiber	Type	Weighted T1/2 fibers L > 20 μm (days)	Reference
Fiber B	B01.9	2.4	Bernstein et al., 1996
Fiber A	Glass wool	3.5	Bernstein et al., 1996
Fiber C	Glass wool	4.1	Bernstein et al., 1996
Fiber G	Stone wool	5.4	Bernstein et al., 1996
MMVF34	HT stone wool	6	Hesterberg et al, 1998
MMVF22	Slag wool	8	Bernstein et al., 1996
Fiber F	Stone wool	8.5	Bernstein et al., 1996
MMVF11	Glass wool	9	Bernstein et al., 1996
Fiber J	X607	9.8	Bernstein et al., 1996
MMVF11	Glass wool	13	Bernstein et al., 1996
Fiber H	Stone wool	13	Bernstein et al., 1996
MMVF10	Glass wool	39	Bernstein et al., 1996
Fiber L	Stone wool	45	Bernstein et al., 1996
MMVF33	Special-purpose glass	49	Hesterberg et al., 1998
RCF1a	Refractory ceramic	55	Hesterberg et al., 1998
MMVF21	Stone wool	67	Hesterberg et al., 1998
MMVF32	Special-purpose glass	79	Hesterberg et al., 1998
MMVF21	Stone wool	85	Bernstein et al., 1996
Amosite	Amphibole asbestos	418	Hesterberg et al., 1998
Crocidolite	Amphibole asbestos	536	Bernstein et al., 1996

Table 10: Harmonised classification under CLP of man-made vitreous fibres.[18]

Index No	International Chemical Identification	Hazard Class and Category Code(s)	Hazard statement Code(s)
650-016-00-2	Mineral wool, with the exception of those specified elsewhere in this Annex; [Man-made vitreous (silicate) fibres with random orientation with alkaline oxide and alkali earth oxide (Na_2O +K_2O+CaO+MgO+BaO) content greater than 18 % by weight]	Carc. 2	H351
650-017-00-8	Refractory Ceramic Fibres, Special Purpose Fibres, with the exception of those specified elsewhere in this Annex; [Man-made vitreous (silicate) fibres with random orientation with alkaline oxide and alkali earth oxide (Na_2O+K_2O+CaO+MgO+BaO) content less or equal to 18 % by weight]	Carc. 1B	H350i

Another factor that influences the persistence of fibres is their diameter. A few studies considered the durability and toxicity of fibres with the same composition, but different diameters. The half-life was proportional to the diameter (3x thicker ~ 3x longer half-life), as would be expected if solubility is proportional to surface area. This resulted in a corresponding increase in tumour rates in rats after intraperitoneal exposure [19].

It should also be considered that reviews of epidemiological studies failed to find a relationship between exposure to MMMFs and the incidence of mesothelioma in humans. This was explained mainly by

their low biopersistence after inhalation, in combination with much lower doses than used in the intraperitoneal studies.[11, 20]
Also various inhalation studies with rock- and slagwool in rats failed to show a significant increase in tumour incidence. Based on these results, the IARC has removed glass, rock, and slagwool fibres from its list of substances "possibly carcinogenic to humans" (Group 2B) in 2002. The IARC Monograph's working group concluded only the more biopersistent materials should remain classified as such. These include refractory ceramic fibres, which are used industrially as insulation in high-temperature environments such as blast furnaces, and certain special-purpose glass wools not used as insulating materials.
It must be emphasized that in their regrading of MMMFs, the IARC weighted the natural exposure route (inhalation) far more than intraperitoneal studies, and this heavily influenced the working groups' decisions.

6.6 Foreign body reactions

As mentioned in the previous sections, the fibres found on the breast implants are larger than the inhalable fibres normally considered in fibre toxicity studies/evaluations. Therefore, the results observed after exposure of small fibres to animals as discussed in chapter 5.2 may not be representative. Thus in addition to the toxicity of fibres, also the physiological response to foreign objects in general should be considered.

The foreign body response is similar for all exogenous materials, including fibres and implants, which remain incorporated and undigested. Host reactions following implantation of materials include injury, blood-material interactions, provisional matrix formation, acute inflammation, chronic inflammation, granulation tissue development, foreign body reaction, and fibrosis/fibrous capsule development.

Experiments in which polymer fibres with different diameters were implanted subcutaneously indicated that capsule formation occurred when the diameter of the fibres was 6 µm or more.[21] This indicates that also the majority of the fibres on the implants, with a mean diameter of 8-10 µm, may induce foreign body reactions. On the other hand, the inhalable fibres which are usually tested in toxicity studies have diameters below 3 µm.
The difference between frustrated phagocytosis and a foreign body reaction on a larger object is that in the latter case, foreign body giant cells are formed at the surface of the objects by merging of macrophages and monocytes. These giant cells as well as macrophages release reactive oxygen species, enzymes and acids.[22] These processes can induce tumour formation, although the specific risk depends on the characteristics of the object such as composition and surface area. Generally, foreign body induced tumours have very low incidence rates and long latency times (typically ~20 years in humans) [23]. Implants in rodents induce tumours after subcutaneous implantation. This type of tumour formation is considered specific for rodents and not relevant for humans and is designated solid state carcinogenesis [24, 25].

6.7 Dose-response relationship

Inflammation/fibrosis
The Scientific Committee on Occupational Exposure Limits (SCOEL) derived threshold values for worker inhalation exposure to MMMFs. The OELs (Occupational Exposure Limits) for rock and slagwool derived were 3 fibres/ml. With an inhalation volume of 10 m^3 per 8-hour working day, this equates to $3*10^7$ fibres/day. These OELs were based on NOAELs for rockwool and slagwool of 30 respirable fibres/ml air from a long-term inhalation study (2-years) by McConnell et al (1994). An assessment factor of 10 was used to derive the OEL from the NOAEL. Exposure to these fibres above the NOAEL induced a dose-related inflammatory response, while rockwool produced minimal focal pulmonary fibrosis in addition to inflammatory response. Both rockwool and slagwool did not induce any neoplastic activity in the lungs or the pleura.[26]
Furthermore, the SCOEL wrote a recommendation for RCFs, for which the evidence for carcinogenicity by inhalation is stronger. For these fibres, an OEL of 0.3 fibres/ml air was derived based on a study in workers in which decrease in lung function was used as critical endpoint. At this concentration no adverse effects were observed. This assessment assumes that there is a threshold for non DNA-reactive carcinogens, such as fibres SCOEL concluded inflammation to be the underlying effect of fibre carcinogenicity, and considered the observed genotoxicity to be only secondary to that, allowing a threshold approach.[27]

For the risk assessment it is proposed to use $3*10^7$ fibres/day as a limit for fibrosis/inflammation, as these were the health effects on which SCOEL based the OEL.

Carcinogenesis
In addition, the risk for carcinogenesis will be assessed, although the available epidemiological studies did not show an increase in tumour incidence after occupational exposure to MMMFs, and also the evidence of animal studies suggest the carcinogenic potential of MMMFs after inhalation is weak. As conservative approach, a non-threshold mechanism of carcinogenicity will be assumed.

Very little information is available on the dose response characteristics of MMMF induced carcinogenesis. Most studies focus solely on whether fibres are carcinogenic or not, in which case the WHO benchmark dose for intraperitoneal studies of $1*10^9$ fibres is usually tested.[16]

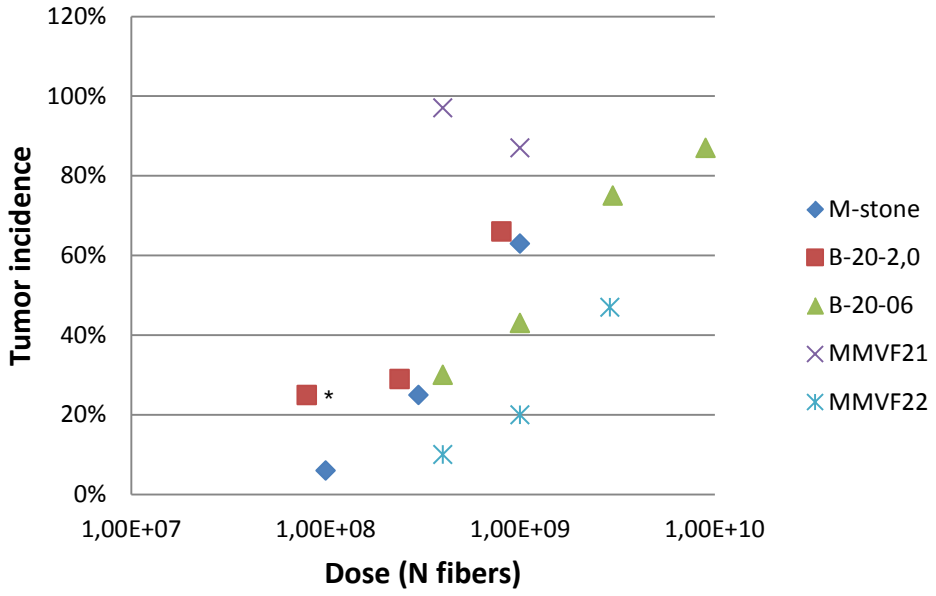

Figure 14. Overview of the results of carcinogenicity studies on the intraperitoneal injection of fibres of rock (stone) and slagwool in rats. Rock/stone wool: M-stone, B-20-2.0, B-20-06, MMVF21; Slagwool: MMVF21.[11] *The data point marked with an * is used for the calculation of the T25.*

In IARC Monograph 81 (2002), a table with carcinogenicity studies using intraperitoneal injection of fibres of rock (stone) and slagwool in rats is provided (page 211-219 of the monograph).[11] The results of rock/ slagwools with multiple concentrations from Davis et al. and Roller et al. (1996) as cited in IARC (2002) are summarized in Figure 14. Both studies were performed with inhalable particles, with a diameter of <3 µm and a length of 3.6-30 µm. Typical doses were in the range of 10^7-10^{10} fibres. The studies summarized used 35-68 animals per dose level and had an observation time of 130 weeks.

The incidence of mesotheliomas in the peritoneal cavity was in the same range as those reported by Miller et al (1999) discussed earlier. As these studies show, the tumour incidence of rockwool goes from approximately 20% at 10^8 fibres to 70% at 10^9 fibres. Again, slagwool is less potent by approximately a factor 2-3 (IARC 2002).[11]

To extrapolate these high doses to the risk at a low dose, a linearised approach is used, which is described in the REACH Guidance, Chapter R8.[28] First, the T25 (defined as the chronic dose that will give 25% of the animals tumours at a specific tissue site after correction for spontaneous incidence, within the standard life time of that species) is calculated by linear extrapolation, using the lowest dose that gives a significant increase in tumour incidence. As can be seen in Figure 14 , this is a dose of $8*10^7$ rockwool fibres (type B-20-2.0), at which the tumour incidence was 25% (the dose marked with an *). The controls in the same study had a tumour incidence of 1 out of 162, or 0.6%. The corresponding T25 is $8*10^7*(0.25/((0.25-0.006)*(1-0.006))) = 8.25*10^7$ fibres.

As the animals were dosed by intraperitoneal injection and the effect is local, no allometric scaling factor (assessment factor for differences in metabolic rate between species) has to be used. This means that the rat T25 is equal to the human T25.
The resulting risk/fibre is 0.25/T25 = $0.25/8.25*10^{7}$ = $3.03*10^{-9}$

6.8 Risk analysis

The fibres that have been found on the breast implants of Silimed vary in composition, but the majority consists most likely of rockwool and/or slagwool fibres. The fibres are exceptionally large, with a median length of ~200 µm and a diameter of approximately 9 µm.
In a study by TÜV SÜD, the highest numbers of fibres were 73 large fibres/implant and 1440 small fibres/implant found on textured implants. As a worst-case estimate, it is assumed that also the small fibres are mineral fibres with a length ≥20 µm. The highest total exposure, assuming two textured breast implants, will be $3*10^{3}$ fibres. For the risk assessment, it is assumed that the fibres remain in the body when the breast implants are removed.

Internal exposure to fibres and other foreign particles can induce chronic inflammation reactions, which in time can lead to the formation of fibrosis and granuloma. These adverse effects may only occur if the fibres are biopersistent and too large to be cleared by macrophages. The risk on the occurrence of these effects depends principally on the dose, durability, rigidity, and dimensions of the fibres.

The main focus of concern to humans has always been on adverse effects following inhalation of fibres. In the data available for this risk assessment, no studies were identified that investigated fibres of similar (non-inhalable) size as have been found on the breast implants, nor studies using chronic intra-muscular/intra-mammary exposure. Also the classifications by the European Commission and IARC, as well as the OELs, focus solely on the hazard/risk caused by inhalation. For this risk assessment, the hazard of large fibres implanted in the breast tissue therefore has to be extrapolated from results of inhalation and intraperitoneal studies. As the mechanism of toxicity of fibres (frustrated phagocytosis and regular foreign body reactions with encapsulation) is similar in the breast and intraperitoneal cavity, it is assumed that the effects and potency will be comparable.

To assess the risk for fibres inflammation and fibrosis, the limit of $3*10^{7}$ fibres/day is taken, based on the OEL of 3 fibres/ml derived for rock and slagwool fibres[26]. Only a fraction of this will be deposited deep in the lungs, where it will do the most harm. An article by Asgharian and Yu (1988) indicates that the deposition of inhalable fibres in the alveoli is at least 5%.[29] Assuming 5% alveolar deposition, the limit of $3*10^{7}$ fibres/day corresponds with a daily dose of $1.5*10^{6}$ and a life-time dose of $1.5*10^{6}$ x 5 days/week x 48 weeks x 40 years = $1.44*10^{10}$ deposited fibres. Comparing this to the worst-case exposure via the breast implants of $3*10^{3}$ fibres, it can be concluded that the latter is far below the lifetime exposure that poses a risk for fibrosis/inflammation in the lungs. Even considering there may be differences between lung and breast tissue, the risk will be minimal. In addition, comparable reactions

can be expected towards the implant itself, which means the additional reaction to the fibres is probably insignificant.

For carcinogenicity, the risk per unit dose level of $3.03*10^{-9}$ results in a cancer risk of $9.09*10^{-6}$ (9 in a million or 0.0009%) for the exposure to $3*10^{3}$ fibres from the Silimed SBI.
If the unidentified small straight fibres are not included in the risk assessment, but only the fibres which have been identified as mineral fibres, the cancer risk is $4.42*10^{-7}$ (4.4 in 10 million or 0.000044%) for exposure to 146 fibres.
The risk which is generally considered acceptable for the general population is $1*10^{-6}$ or 1 in a million. This is equivalent to the implantation of 330 fibres. If the worst-case assumption is taken that also the small fibres are mineral fibres ≥20 µm, the risk is slightly above one in a million, while if only the identified mineral fibres are taken into account, the risk is slightly below this level.

Of course, these numbers are subject to many uncertainties. Worst case assumptions had to be made in all cases where the information was incomplete (number of fibres, type of fibres included in calculation, assuming there is no threshold for carcinogenicity and using the most potent form of MMMF). The rockwool fibres, on which the carcinogenicity risk is based, are more potent than other MMMFs owing to their persistence. Currently, it is unclear to which type of wool the fibres on the implants belong, but it is likely to be a mixture of fibres which on average are expected to be less potent than the worst case assumed in the calculation for the relatively persistent rockwool.
It is also unknown how the tumour risk in breast/muscle tissue compares to that of the intraperitoneal cavity. Although the mechanism is the same, the intensity of the inflammatory response and the sensitivity of the cells for oxidative stress may be different. Also, if any tumours are formed, these will probably be sarcomas instead of the mesotheliomas observed after inhalation/intraperitoneal exposure. This is because mesotheliomas can only develop in the mesothelium, usually the pleura after inhalation or the peritoneum after intraperitoneal exposure. The fibres on the breast implants will probably be incorporated in muscle or fat tissue, which may form sarcomas.
Further, it is unknown what is the effect of the increased length and diameter of the Silimed fibres in comparison with those in the toxicity studies. It may lead to a higher toxicity through an increase in persistence, but might as well result in a lower toxicity if they are encapsulated because of their large size.

7 Discussion and conclusion

The TÜV SÜD and RMS reports describe that MMMF were found on the surface of several Silimed textured SBI and Silimed tissue expanders manufactured between 2013 and 2015. The present report shows that MMMF contamination also affected Silimed PU-coated SBI and that MMMF contamination was already existent as early as 2009. Silimed SBI may contain two types of MMMF simultaneously. In addition to the two types of MMMF found on Silimed SBI, several other foreign particles were identified on Silimed PU-coated SBI that were not found on Silimed textured SBI and vice versa. The 'small straight fibres' reported by TÜV SÜD were not observed on any of the SBI examined at RIVM.

Because the MMMF were not homogeneously distributed over the SBI surface area, the number of MMMF found on the 6 SEM pads may not be representative for the total number on the SBI surface. This also means that, considering the sample size, considerable uncertainty in the estimate of the number of fibres should be anticipated. A larger sample size and sampling area would provide a more accurate figure on frequency and exposure but this would probably not considerably improve the worst-case approach in the risk analysis which used the highest number of MMMF found on 6 SEM pads.

TÜV SÜD has indicated that Silimed SBI and tissue expanders were manufactured in different buildings. Because both were contaminated with similar MMMFs this indicates a common source of contamination. There is no apparent explanation for the unusual foreign particles on Silimed PU-coated SBI tentatively identified as spherical glass and siliciumcarbide.
Screening of the primary packaging indicated that MMMF preferred to adhere to the SBI rather than to the packaging. Considering the high dielectric value of silicones, an electrostatic charge on the SBI may be responsible for attracting MMMF and other particles present in the production environment.

A third type of MMMF was observed on a comparator SBI manufactured by Brand C. These MMMF were present in similar numbers, yet slightly curved and some were found in clusters. A formal risk analysis is not possible because of the small sample-size. Additional studies are necessary to assess the health risk analysis for those fibres.

The observation of a fluoro-rich particle, possibly Teflon, on a Brand C SBI brings about a similarity with the Silimed case where TÜV SÜD reports: "*The conveyer belt of the drying tunnel consists of Teflon coated glass fibre material. However, the implants do not have direct contact to the conveyer belt*".[4] Nevertheless, an electrostatically charged SBI would attract MMMF and other particles without requiring direct contact. Therefore, conveyor belts, whether part of a drying tunnel or not, should be reconsidered as a potential source of MMMF contamination. In addition, the manufacturers' measures to prevent an SBI from becoming electrostatically charged during production should be reviewed.

This risk analysis was carried out on the same data as the earlier risk analysis commissioned by Silimed (Exponent report).[5] Exponent, like Silimed,[2] does also count the ‘small straight fibres’ as MMMF but does not treat the MMMF as substances "possibly carcinogenic to humans". However, as discussed in 5.5, this viewpoint essentially applies to inhalable particles. Animal studies showed that glasswool, rockwool and slagwool fibres do have a carcinogenic potential after intraperitoneal injection. Therefore, the RIVM risk analysis considers the MMMF as possibly carcinogenic after implantation. For carcinogenicity, the risk is very small and around the acceptability limit of 1 in a million. The risks for inflammation and fibrosis are probably insignificant. As described in 5.8, the health risk analysis is subject to the many uncertainties.

A remaining question is whether actions are warranted with regard to patients with potentially contaminated implants. In principle, this is a joint decision to be taken by the patient and the treating physician. Two considerations can be given: 1) it is unlikely that implanted MMMF can be removed after implantation at all. 2) the risks of the medical procedure necessary for SBI explantation (or replacement) are considerable.

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9 References

[1] RMS. Residue Analysis on Mammary Implants and Tissue Expanders A Summary. **2015**.

[2] Silimed. Critical analysis ACR-116, Risk analysis to the patient due to the presence of particles on the surface of Silimed implants.

[3] TÜV SÜD. Analysis of particulate contamination on textured, smooth, and polyurethane coated mammary implants. **2015**.

[4] TÜV SÜD. Summary of events regarding Silimed. **2015**, .

[5] Exponent. Toxicological Risk analysis of Foreign Material Detected on SILIMED Silicone Breast Implants. **2015**.

[6] SCENHIR. The safety of Poly Implant Prothèse (PIP) Silicone Breast Implants Update of the Opinion of February 2012. **2014**.

[7] P.H.J. Keizers, M.J. Vredenbregt, F. Bakker, D. de Kaste, B.J. Venhuis. Chemical fingerprinting of silicone-based breast implants. *J. Pharm. Biomed. Anal.* **2015**, *102*, 340-345.

[8] WHO. Environmental Health Criteria 77, Man-Made Mineral Fibers. *International programme on chemical safety* **1988**.

[9] personal communication with TÜV SÜD

[10] S.A. Miller BG, Davis JM, Donaldson K, Cullen RT, Bolton RE, Buchanan D, Soutar CA. Influence of fibre length, dissolution and biopersistence on the production of mesothelioma in the rat peritoneal cavity. *The Annals of occupational hygiene* **1999**, *43*, 155-166.

[11] IARC. Monograph 81: Man-made Vitreous Fibres. **2002**.

[12] IARC. Monograph 43: Man made mineral fibers and radon. **1988**.

[13] IntensiveTutorialService. Available at: http://intensivetutorial.com/doc/image/school_maths_formulae/Formula-Mensuration-Hemisphere-Volume%20and%20surface%20area%20and%20curved%20surface%20area-1.jpg [02-11-2015]

[14] Donaldson K, Murphy FA, Duffin R, Poland CA. Asbestos, carbon nanotubes and the pleural mesothelium: a review of the hypothesis regarding the role of long fibre retention in the parietal pleura, inflammation and mesothelioma. *Particle and Fiber Toxicology* **2010**, *7*.

[15] Krombach F, Munzing S, Allmeling AM, Gerlach JT, Behr J, Dorger M. Cell size of alveolar macrophages: an interspecies comparison. *Environmental health perspectives* **1997**, *105*, 1261-1263.

[16] Bernstein DM. Synthetic Vitreous Fibers: A Review Toxicology, Epidemiology and Regulations. *Critical Reviews in Toxicology* **2007**, *37*, 839-886.

[17] W. Eastes, R.M. Potter, J.G. Hadley. Estimating in vitro glass fiber dissolution rate from composition. *Inhalation Toxicology* **2000**, *12*, 269-280.

[18] EC Regulation No 1272/2008 of the European parlement and of the council on classification, labelling and packaging of substances and mixtures. **2008**.

[19] Brown RC, Hoskins JA, Johnson N. in *Mechanisms in Fibre Carcinogenesis*, NATO ASI Series, Series A, Life Sciences (Vol 223), **1991**.

[20] Boffetta P, Donaldson K, Moolgavkar S, Mandel JS. A systematic review of occupational exposure to synthetic vitreous fibers and mesothelioma. *Critical Reviews in Toxicology* **2014**, *44*, 436-449.
[21] Sanders JE, Cassisi DV, Neumann T, Golledge SL, Zachariah SG, Ratner BD, Bale SD. Relative influence of polymer fiber diameter and surface charge on fibrous capsule thickness and vessel density for single-fiber implants. *Journal of biomedical materials research. Part A* **2003**, *65*, 462-467.
[22] Anderson JM, Rodriguez A, Chang DT. Foreign body reaction to biomaterials. *Semin Immunol* **2008**, *20*, 86-100.
[23] Okada F. Beyond foreign-body-induced carcinogenesis: Impact of reactive oxygen species derived from inflammatory cells in tumorigenic conversion and tumor progression. *Int. J. Cancer* **2007**, *121*, 2364-2372.
[24] Bischoff F, Bryson G. Carcinogenesis through solid state surfaces. *Prog Exp Tumor Res* **1964**, *5*, 85-133.
[25] Kirkpatrick CJ, Alves A, Köhler H, Kriegsmann J, Bittinger F, Otto M, Williams DF, Eloy R. Biomaterial-induced sarcoma: A novel model to study preneoplastic change. *Am J Pathol* **2000**, *156*, 1455-1467.
[26] SCOEL. Recommendation from the Scientific Committee on Occupational Exposure Limits for man-made mineral fibres (MMMF) with no indication for carcinogenicity and not specified elsewhere. **2012**.
[27] SCOEL. Recommendation from the Scientific Committee on Occupational Exposure Limits for Refractory Ceramic fibres. **2010**.
[28] ECHA. Guidance on information requirements and chemical safety assessment *Chapter R.8: Characterisation of dose [concentration]-response for human health* **2012**.
[29] Asgharian B, Yu CP. Deposition of inhaled fibrous particles in the human lung. *Journal of aerosol medicine* **1988**, *1*, 37-50.

10 Appendix 1 Samples

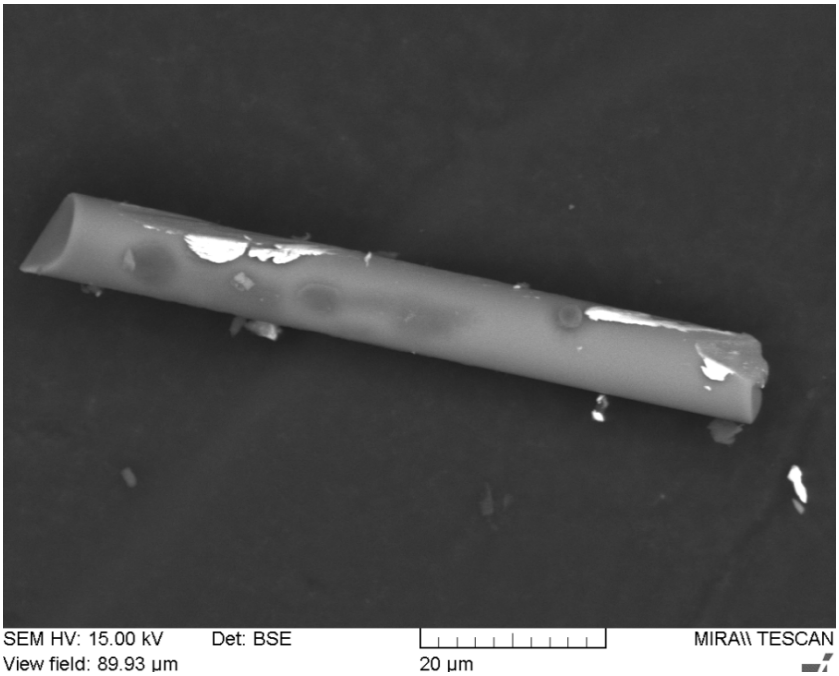
RIVM sample number	Manufacturer	Type	Serial number	Date received
A090401	Silimed	30646-485XH	5709434	2015-09-22
A090402	Silimed	30646-485XH	5709433	2015-09-22
A090801	Silimed	30637-360HI	5300351	2015-10-08
A090802	Silimed	30637-410HI	5236259	2015-10-08
A090803	Silimed	30637-245MD	4376903	2015-10-08
A090804	Silimed	20622-505HI	4412189	2015-10-08
A090805	Silimed	30646-255 LO	3860328	2015-10-08
A090806	Silimed	30645-370L	3424208	2015-10-08
A090807	Silimed	30674-240MD	4546969	2015-10-08
A090808	Silimed	30637-360HI	5695107	2015-10-08
A090809	Silimed	30622-305HI	5051250	2015-10-08
A090810	Silimed	30674-315MD	4675401	2015-10-08
A091401	Silimed	20637-205MD	5285171	2015-10-13
A091402	Silimed	20637-205-MD	5251212	2015-10-13
A091403	Silimed	20637-205-MD	5048718	2015-10-13
A091404	Silimed	20637-220HI	4973047	2015-10-13
A091405	Silimed	20637-170MD	4623879	2015-10-13
A091406	Silimed	20637-205MD	5395952	2015-10-13
A091407	Silimed	20637-170MD	5127120	2015-10-13
A091408	Silimed	20637-220HI	5293381	2015-10-13
A091409	Silimed	30637-200HI	4366997	2015-10-13
A091410	Silimed	30535-245MD	4373478	2015-10-13
A091411	Silimed	30646-345HI	5713114	2015-10-13
A091412	Silimed	30535-245MD	4427760	2015-10-13
A091413	Silimed	30646-345HI	5705385	2015-10-13
A091414	Silimed	30535-245MD	5295541	2015-10-13
A091415	Silimed	30637-200HI	522206	2015-10-13
A091416	Silimed	30622-330HI	5727900	2015-10-13
A091417	Silimed	30622-280HI	5181489	2015-10-13
A091418	Silimed	30622-280HI	5239949	2015-10-13
A091419	Silimed	30622-330HI	5451770	2015-10-13
A091420	Silimed	30535-245MD	4373488	2015-10-13
A091421	Silimed	20637-220HI	4312538	2015-10-13
A091422	Silimed	20622-285HI	4123261	2015-10-13
A091423	Silimed	20637-220HI	4312539	2015-10-13
A091424	Silimed	20622-285HI	4123263	2015-10-13
A091425	Silimed	20637-205MD	4349836	2015-10-13
A091426	Silimed	20637-205MD	4293459	2015-10-13
A091427	Silimed	20622-285HI	3881778	2015-10-13
A091428	Silimed	20637-220HI	4312537	2015-10-13

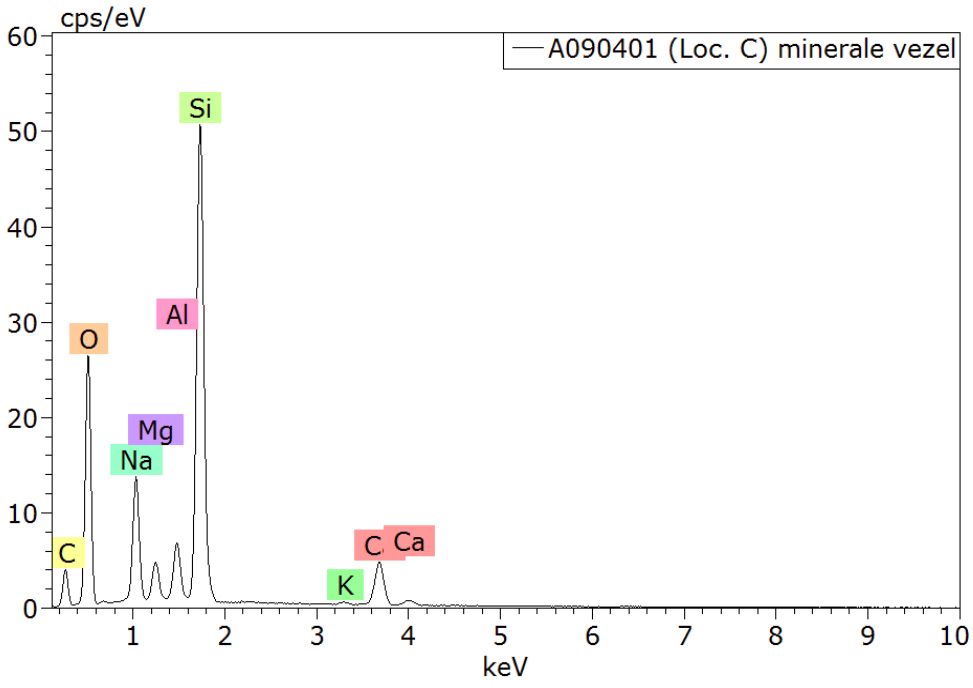
RIVM sample number	Manufacturer	Type	Serial number	Date received
A091429	Silimed	20622-285HI	4123262	2015-10-13
A091430	Silimed	20637-220HI	4308217	2015-10-13
A091431	Silimed	30622-255MD	5181334	2015-10-13
A091432	Silimed	20622-330MD	5373158	2015-10-13
A091433	Silimed	20622-330MD	4799321	2015-10-13
A091801	Silimed	20646-350XH	5801938	2015-10-21
A091802	Silimed	20622-305HI	5540618	2015-10-21
A091803	Silimed	20637-270HI	5813643	2015-10-21
A091804	Silimed	20646-285LO	5580187	2015-10-21
A091805	Silimed	20622-240MD	5423560	2015-10-21
A091806	Silimed	20646-280XH	5401338	2015-10-21
A091807	Silimed	20674-375XH	5716607	2015-10-21
A091808	Silimed	20622-245HI	5825811	2015-10-21
A091809	Silimed	20622-280MD	5814497	2015-10-21
A091810	Silimed	20622-170LO	5477365	2015-10-21
A092701	Silimed	20622-305XH	5491581	2015-11-09
A092702	Silimed	20622-390HI	5532655	2015-11-09
A092703	Silimed	20637-360MD	5729945	2015-11-09
A092704	Silimed	20637-270HI	5539004	2015-11-09
A092705	Silimed	20622-330MD	5441773	2015-11-09
A091601	Brand A			2015-10-16
A091602	Brand A			2015-10-16
A091603	Brand A			2015-10-16
A091604	Brand A			2015-10-16
A091605	Brand A			2015-10-16
A091606	Brand A			2015-10-16
A091607	Brand A			2015-10-16
A091608	Brand A			2015-10-16
A091609	Brand A			2015-10-16
A091610	Brand A			2015-10-16
A091611	Brand A			2015-10-16
A091612	Brand A			2015-10-16
A091613	Brand A			2015-10-16
A091614	Brand A			2015-10-16
A091615	Brand A			2015-10-16
A092101	Brand B			2015-10-29
A092102	Brand B			2015-10-29
A092103	Brand B			2015-10-29
A092104	Brand B			2015-10-29
A092401	Brand C			2015-11-02
A092402	Brand C			2015-11-02
A092403	Brand C			2015-11-02
A092404	Brand C			2015-11-02

RIVM sample number	Manufacturer	Type	Serial number	Date received
A092405	Brand C			2015-11-02

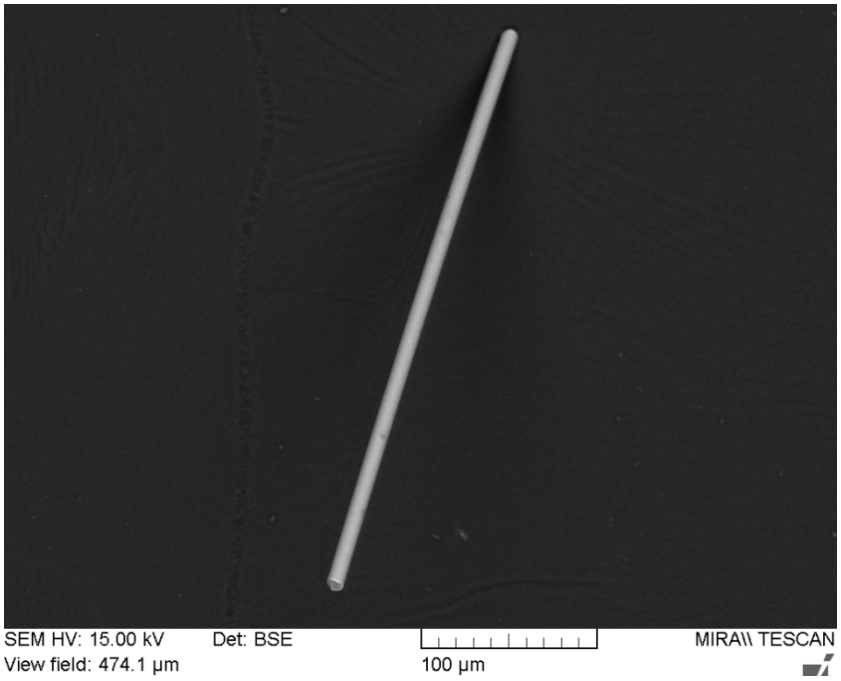
11 Appendix 2 Exemplary SEM images

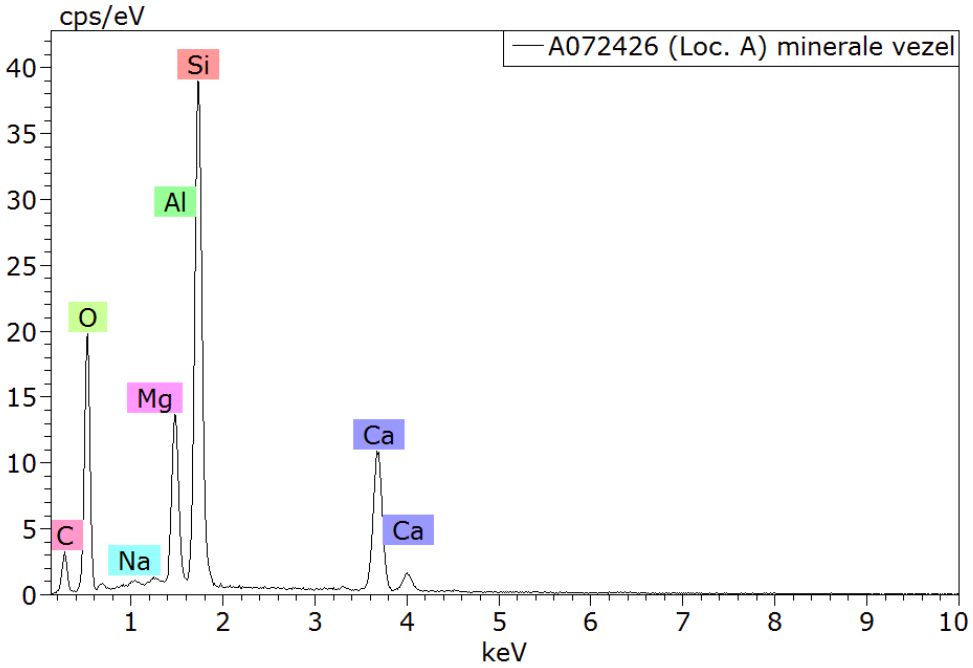
MMMF type 1, diameter ±2-10 µm, length ±20-80 µm



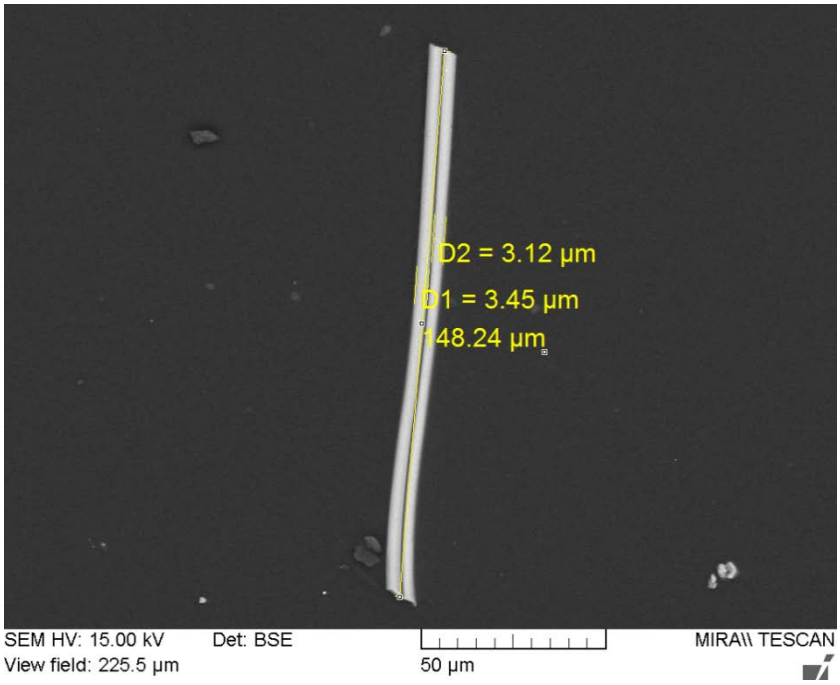


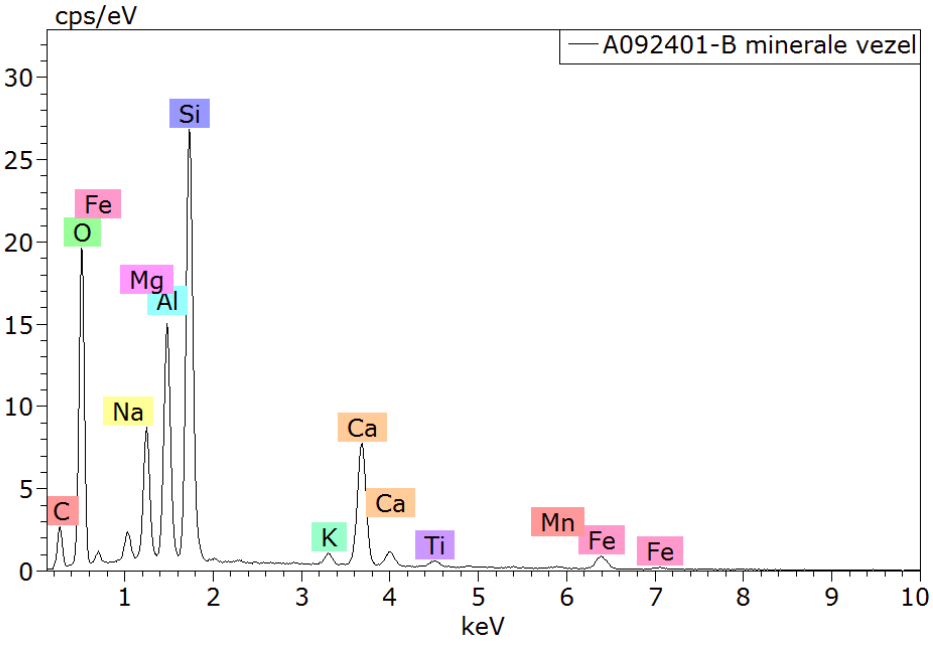
MMMF type 2, diameter ±6-10 µm, length ±20-400 µm



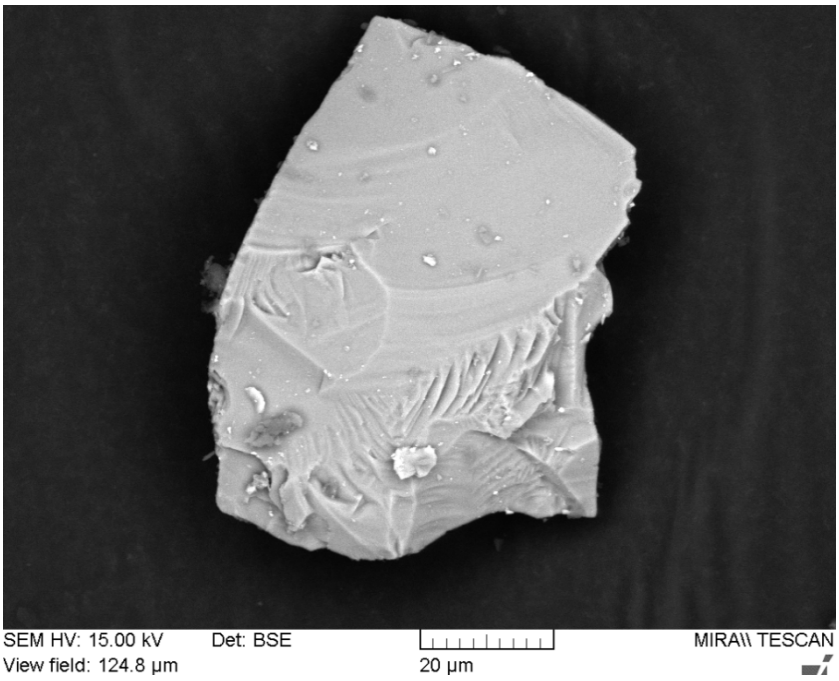


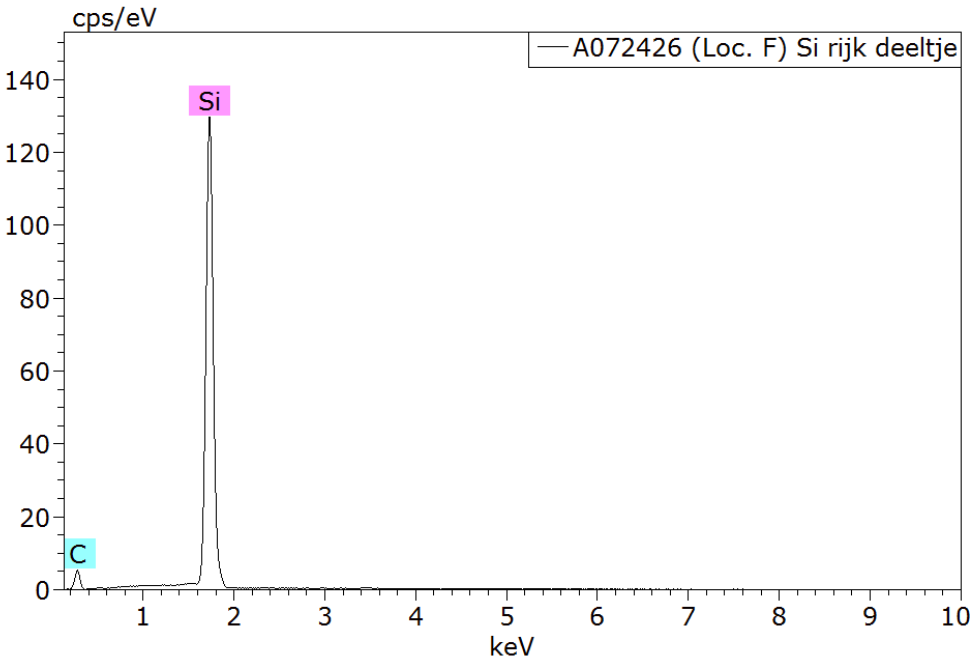
MMMF type 3, diameter ±1-8 µm, length ±60-500 µm



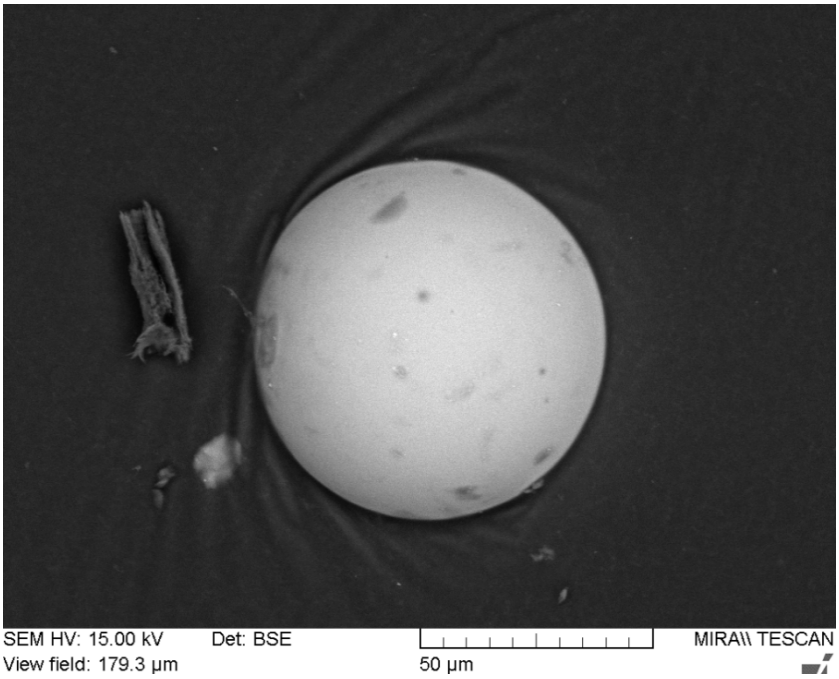


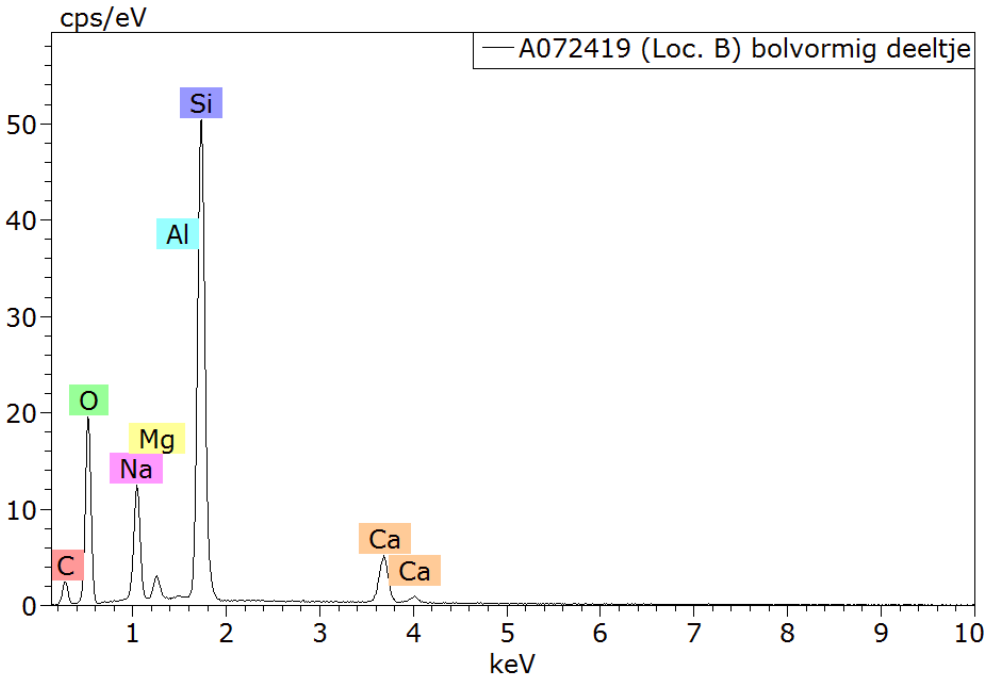
Silicon-rich particle



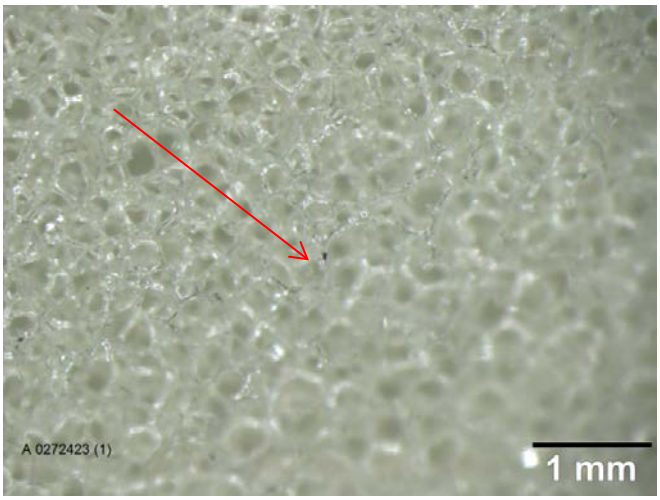


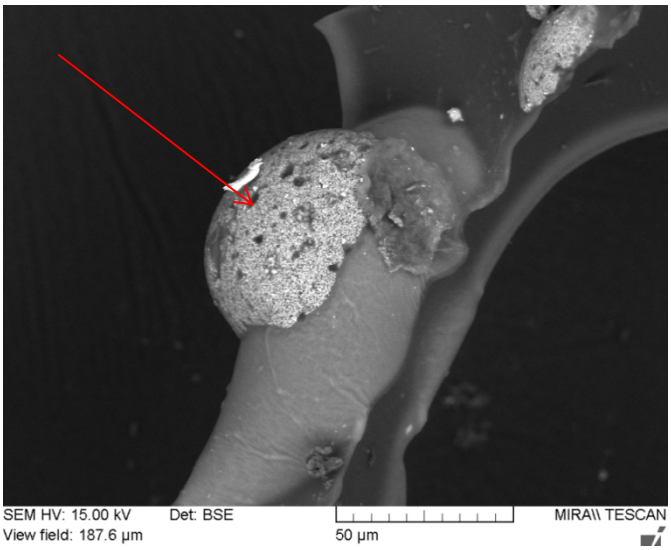
Spherical glass-like particle, diameter ±20-100 µm

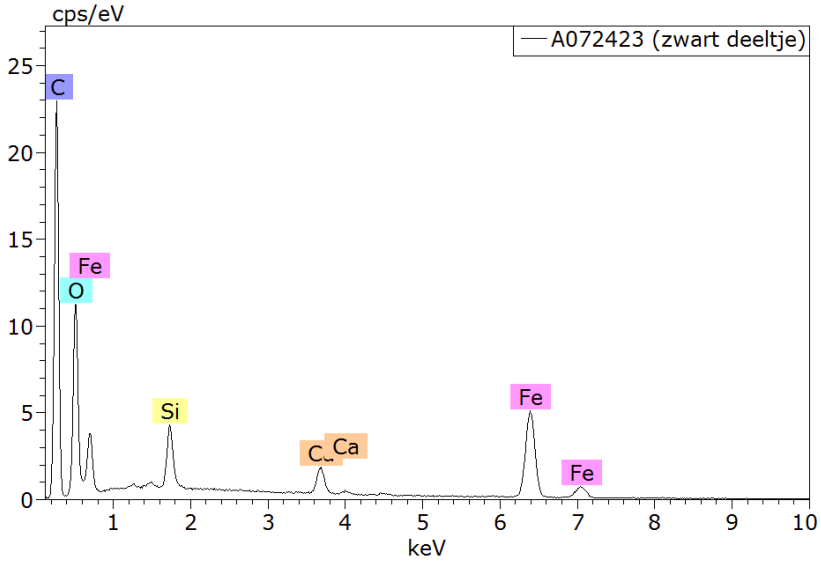




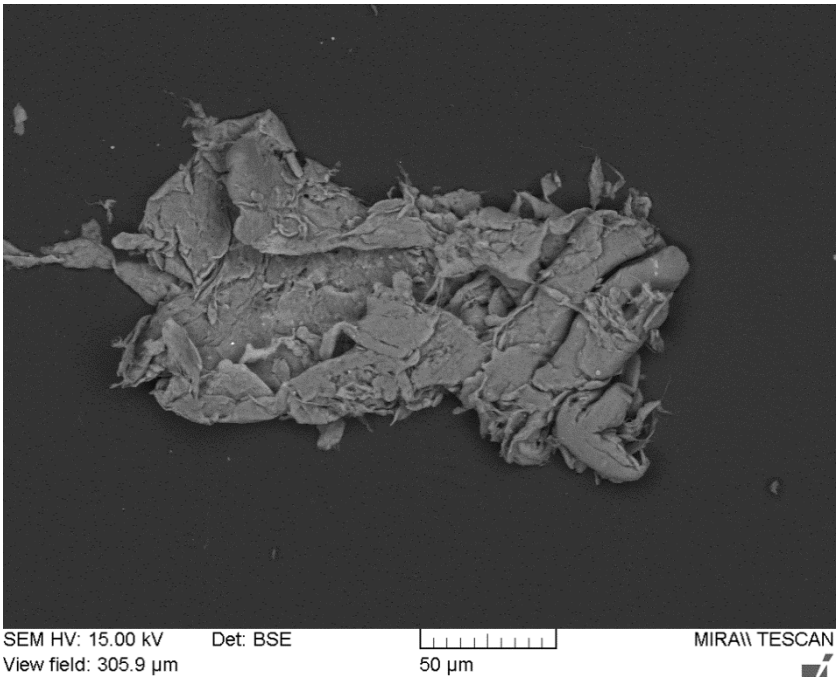
Iron-rich particle embedded in the PU-coating (visible to the naked eye)

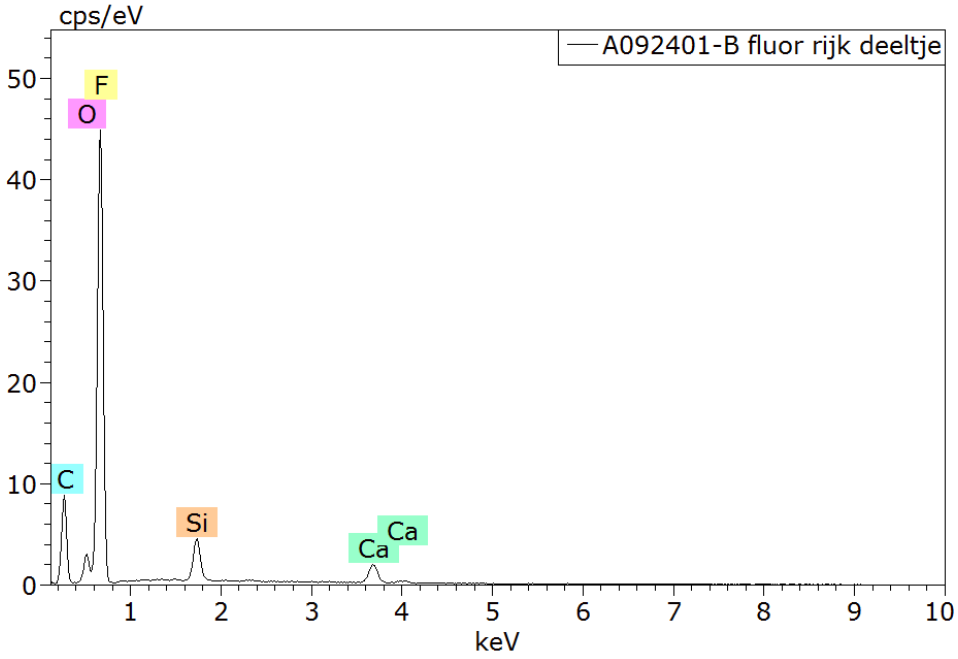




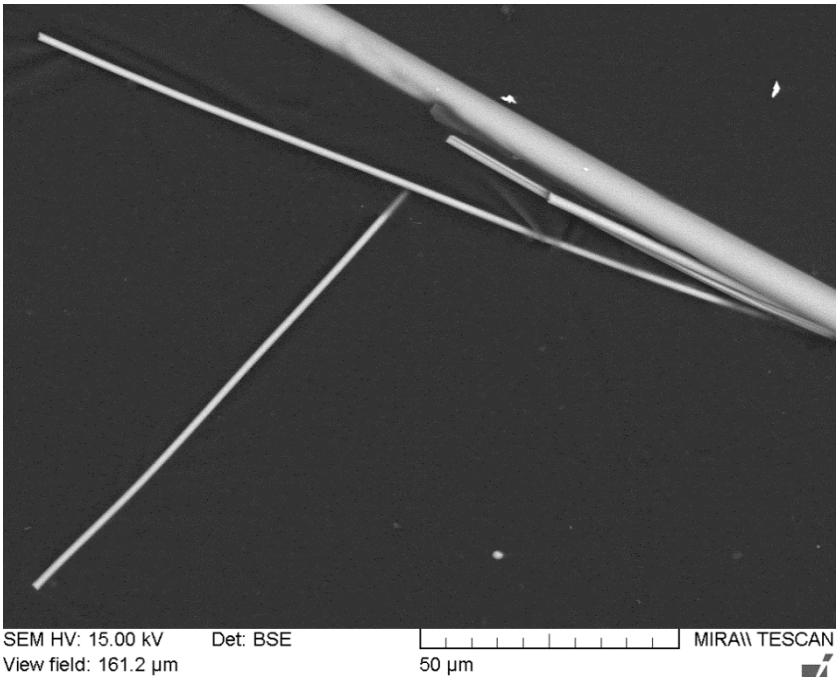


Fluor-rich particle found on Brand C SBI





Cluster of MMMF type 3 found on Brand C SBI



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