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Toxicological Risk Assessment of Foreign Material Detected on SILIMED Silicone Breast Implants

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LIMITATIONS

The purpose of this report is to assess the clinical impact to the patient of the foreign particles observed on the SILIMED breast implants. This assessment is based on review of analytical results presented in the following reports[1]:

> TÜV SÜD. 2015. *Analysis of particulate contamination on textured, smooth, and polyurethane coated mammary implants.* Report UAA PS order number 713061556. Industrie Service order number 600014710. July 28, 2015.
>
> SILIMED. 2015. *Critical analysis. Risk analysis to the patient due to the presence of particles on the surface of SILIMED implants.* ACR-116. September 4, 2015.

The risk assessment addresses three separate types of materials found on the implants: particles (assumed to be polydimethylsiloxanes), glass and textile fibers, and silver. The findings presented herein are made to a reasonable degree of scientific certainty in accordance with generally accepted risk assessment practices using conservative default assumptions. These conservative assumptions include the following:

- The implants are of the greatest possible surface area and a female patient has a body weight between the 15th and 25th percentile, thus maximizing the potential exposure of the patient to particles and fibers;
- For the particles assessment, the particles in each size bin are of the largest diameter possible and are spherical in shape, thus maximizing the volume of the particles possible; and
- All of the particles and fibers quantified in the SILIMED report are on the surface of the implant, and thus, accessible to the patient.

Given the nature of these evaluations, significant uncertainties (which are inherent in any risk assessment) are associated with the estimation of potential exposure and potential risks. These results of this assessment are not facts or predictions of the risk that may occur. Furthermore, the assumptions adopted in determining these risk estimates do not constitute the exclusive set of reasonable assumptions and use of a different set of assumptions or methodology could produce materially different results.

Exponent reserves the right to supplement this report and to expand or modify the conclusions and findings based on the review of additional materials as they become available through additional work or the review of additional work performed by others.

[1] The initial evaluation of SILIMED breast implants was conducted by RMS and a report produced on July 9, 2015. Some information on the analysis is provided in this report, but none of the details and results of the optical assessments are provided. Counts of particles >100 µm are included in the SILIMED report.

EXECUTIVE SUMMARY

At the request of SILIMED, Exponent has conducted a review of the toxicity and an assessment of the solid foreign material detected on SILIMED's silicone breast implants to evaluate the potential clinical impact to the patient receiving these breast implants. Three separate types of materials have been detected on the implants: particles (assumed to be polydimethylsiloxanes), glass and textile fibers, and silver. Based on various optical evaluations, RMS/TÜV and SILIMED determined the surface concentration of solid foreign material on numerous sample breast implants. Based on these analytical findings and the toxicity of the various materials, Exponent conducted a risk assessment of these materials that included the derivation of margins of exposure for patients potentially exposed to the foreign material on the implants. Each of these margins of exposure incorporates at least a 100-fold safety factor; therefore, a margin of exposure of one or higher is protective of human health.

The margins of exposure for dislodgeable particles as quantified by TÜV range between 48 and 1721. SILIMED conducted their analysis based on a quantification of all particles on the surface of the implant; this method does not distinguish between dislodgeable and embedded particles, which resulted in higher particle counts. The margins of exposure for all particles from the SILIMED analysis ranged from 2 to 28. Thus, the margins of exposure for particles for all samples are greater than one.

The margins of exposure for dislodgeable fibers as quantified by TÜV range between 1112 and 4354. As noted above, SILIMED counted all fibers with the margins of exposure for all fibers ranging from 4 to 162. Thus, the margins of exposure for fibers for all samples are greater than one.

A single silver particle was detected in the TÜV analysis. The margin of exposure for the silver particle is 4.

Exponent's risk assessment of the solid foreign materials observed on SILIMED's breast implants was conducted in a standard and conservative manner. Several factors contribute to the conservative nature of the provided margins of exposure. Many of the exposure assumptions are upper bound and represent a reasonable worst case, including the use of the maximum size breast implant and the body weight of a small woman (15^{th} to 25^{th} percentile). A maximum size was assumed for all particles, including the silver particle. The maximum size incorporated use of a spheroid shape for the volume of the particle as well as use of the largest diameter possible for each particle size bin. It is also assumed that these particles and fibers are all bioavailable. Finally, a safety factor of at least 100-fold has been applied to the derivation of the NSRLs.

As evidenced by the calculated margins of exposure, the presence of particles, textile or glass fibers, and silver on the surface of the SILIMED breast implants at the quantities reported in the TÜV and SILIMED analyses do not pose an unacceptable risk to a patient from the implantation of SLIMED's silicone breast implants.

INTRODUCTION

The Brazilian company SILIMED manufactures breast implants that are sold worldwide. In Europe, TÜV serves as the Notifying Body to ensure the conformity of these implants for sale to the medical community. Earlier this year, on behalf of TÜV SÜD, several breast implant samples were obtained for evaluation of the quality of the SILIMED product, which included an investigation of the potential presence of solid foreign material on the surface of the implants (RMS, 2015). The analysis was conducted using stereomicroscopy, electron microscopy and energy dispersive X-ray (EDX). The analysis identified various size particles, organic fibers and glass fibers. The source of this solid foreign material was thought to be a drying tunnel, which was subsequently put out of service at the SILIMED manufacturing facility. Following this corrective measure, additional sample breast implants were collected in July 2015 and sent to Munich for analysis. Again, solid foreign material was observed on the surface of the implants (TÜV, 2015). Textured surface implants were determined to have a larger number of particles on the surface when compared to the number of particles observed on the polyurethane and smooth-surface type implants. In contrast, fibers were observed at a comparable rate on the textured and polyurethane implants, but fewer fibers were detected on the smooth implants.

Subsequent to these findings, the sale of SILIMED breast implants was halted in Europe pending an evaluation of the potential clinical impact to the patient of the solid foreign material contamination. In July and August 2015, SILIMED conducted their own analysis of sample breast implants collected from the manufacturing facility using the methods outlined in Annex A of the international standard ISO 14607 (SILIMED, 2015). Their analysis confirmed the presence of particles on the surface of the silicone breast implants.

Exponent was requested to review the various evaluations of solid foreign material detected on SILIMED's silicone breast implants and to assess the potential clinical impact to the patient of the observed particles on the breast implants. Exponent examined the toxicity of the various types of materials and conducted a risk assessment to derive margins of exposure for patients potentially exposed to particles and fibers on SILIMED silicone breast implants. This assessment is based on the analytical findings of RMS/TÜV and SILIMED regarding the surface concentration of solid foreign material on sample breast implants which are detailed in the following reports:

> RMS. 2015. *Residue analysis on mammary implants and tissue expanders. A summary.* Report A15_0969_00. Initiation/completion dates: June 1, 2015 to July 9, 2015.
>
> TÜV SÜD. 2015. *Analysis of particulate contamination on textured, smooth, and polyurethane coated mammary implants.* Report UAA PS order number 713061556. Industrie Service order number 600014710. July 28, 2015.
>
> SILIMED. 2015. *Critical analysis. Risk analysis to the patient due to the presence of particles on the surface of SILIMED implants.* ACR-116. September 4, 2015.

These three reports provide the results of three distinct analyses of the SILIMED silicone breast implants. All of the analyses were performed in different laboratories with different types of equipment

and testing methods. For example, RMS performed scanning electron micrography (SEM) of six carbon tape pads that had been pressed to the surface of an implant and then conducted a cursory count of particles and fibers at 50-fold magnification. TÜV conducted their SEM analysis by counting ten 6 mm^2 squares within each of six carbon tape pads at 100-fold magnification. Obviously, the difference in magnification has an impact on the number of particles/fibers identified. This is noted in the conclusions of the RMS report where it is stated that at 50-fold magnification 38 fibers were detected on the surface of one sample, but when the magnification was increased to 160-fold, 576 particles were counted in ¼ of the surface of an implant. In contrast, in the SILIMED SEM analysis, particles and fibers were counted directly on the surface of implant samples at 1800x magnification (SILIMED, personal communication), which does not allow for the distinction between dislodgeable surface particles and embedded particles. Consequently, substantial differences exist in the reported findings for particle and fiber counts and the results are not directly comparable across analyses.

This report provides a brief summary of the data available on the toxicity of the particles, textile fibers, and glass fibers identified in these reports. Based on the known toxicity of these materials, a conservative acceptable dose was determined for each type of material. Using standard, conservative risk assessment methods, these doses were then compared to the potential exposure of a patient to particles, fibers, or silver as present on the implants. The comparison of acceptable doses to the potential exposure estimates are provided as margin of exposure values. Our assessment considers the solid particles and fibers separately. Although only a single particle of silver was identified on one of the sample breast implants in the TÜV analysis, the potential risk from exposure to this quantity of silver is presented below.

TOXICITY OF IDENTIFIED FOREIGN MATERIAL

Three types of material have been identified on the surface of the SILIMED breast implants: particles, fibers, and silver. Based on the results of EDX microanalysis, SILIMED surmised that the particles observed on the implants are polydimethylsiloxanes (PDMS) (SILIMED, 2015). Various fibers were also observed on the breast implants and characterized as glass or textile fibers. In the RMS report, the fibers were identified as being primarily glass; however, the fibers were not quantified. In the TÜV report, glass fibers were identified on the textured implants, but not on the polyurethane or smooth surface implants. Finally, a single silver particle was identified in the analysis. A brief description of the toxicity of these materials is provided below.

Although Exponent's risk assessment is based on chemical-specific data, it should be understood that the biological response to small particles as detected on SILIMED's breast implant is generally due to the physical nature of the material, not the chemical composition. Godleski et al. (1981) implanted 1 mg of either lint containing wood cellulose, cotton fibers, or micropulverized polypropylene and report that the foreign-body response did not differ among the types of materials. Overall, the general health of the animals were not affected and the response was limited to the area of the implanted material where adhesions occurred in a few animals and granulomas occurred in most animals at 32 weeks.

PDMS Toxicity

PDMSs are silicone-based polymers that are the primary component in the manufacture of the breast implant shell. The toxicology of PDMSs has been extensively reviewed by the U.S. National Academy of Sciences (NAS) Institute of Medicine (IOM) (IOM, 1999). The IOM found that "PDMS fluids, gels, and elastomers were generally well tolerated on injection or implantation." While solid state carcinogenesis was been observed in rodents, this process appears to be rodent-specific and occurs with the implantation of a variety of inert materials including silicone, glass and acrylic (IOM, 1999). Based on their review, the IOM concluded that although PDMS can:

> *"induce solid-state carcinogenesis in the susceptible rodent species associated with this phenomenon, it is not a specific response to silicone. Solid-state carcinogenesis occurs in rodents with exposure to a wide array of other substances. There is no convincing evidence that it is a human risk."*

Studies on the distribution in the body of PDMS and other silicones following implantation have found that these materials largely remain where they are implanted (IOM, 1999). However, small amounts of the material (>1%) may be found in lymph nodes draining the implantation site. Thus, it is possible that particles of PDMS that are sufficiently small enough to be phagocytized by macrophages (i.e., <20 µm), may be engulfed and subsequently transported to the lymph nodes to be cleared from the body.

Toxicity of Glass or Textile Fibers

Glass and textile fibers are chemically inert. The toxicity associated with synthetic vitreous fibers like glass is related to the dose (amount of fibers encountered), the dimensions of the fibers (i.e., the overall length of the fibers) and the durability, or biopersistence, of the fibers (Maxim et al., 2006). Fibers under 20 µm may be removed from the body by macrophages, which engulf, or phagocytize the fibers

and carry them to the lymph nodes for clearance from the body. Larger fibers, however, may induce "frustrated phagocytosis," which can cause cytotoxicity and inflammation. Although specific information on textile fibers is not readily available, it is anticipated that textile fibers would be handled by the body in much the same manner as synthetic vitreous fibers. However, textile fibers are likely to be less biopersistent than glass fibers. The SILIMED report provides a relatively thorough discussion of the toxicity associated with both glass and textile fibers and that factors that affect this toxicity (SILIMED, 2015).

Silver Toxicity

Humans are exposed to low levels of silver on a daily basis, with intakes estimated to be 10-88 µg/day (Lai and Ewald 2006). In addition, silver-based medicines have been administered in the past to treat a number of different medical conditions (EPA, 1991).

Deposition of silver in the skin can result in a permanent bluish-gray discoloration of the skin called argyria. The increased pigmentation of the skin becomes more pronounced with exposure to sunlight due to photo-reduction of the metal. Although the change that results is permanent, arygria is not associated with any adverse health effects and is considered to be a medically benign condition. This condition has been the basis for most regulatory standards or exposure limits for silver.

The SILIMED report provides a discussion of the clinical effects associated with silver (SILIMED, 2015). As described in this report, metallic silver is inert in the body, but ionizes in the presence of moisture (e.g., body fluids). Therefore, over time a silver metal particle will release silver ions that will then bind to other compounds or proteins and would be cleared from the body.

RISK ASSESSMENT OF FOREIGN MATERIAL ON SILIMED BREAST IMPLANTS

Particles

No Significant Risk Level (NSRL) for PDMS Particles

No regulatory exposure levels for PDMS were found to support a human health risk assessment. Therefore, for the purposes of this assessment, findings from a 24-month chronic study in rats (UBTL, 1993) were used to derive a NSRL for humans.

In this study, two different types of textured silicone breast implants, a silicone elastomer dispersion (described as a smooth surfaced elastomeric solid sheet) and a responsive silicone gel were implanted into female Fischer 344 rats (n = 60 main study animals + 20 satellite animals per group). To prepare the solid silicone materials for implantation, the shells were frozen in liquid nitrogen, then pulverized using a Waring blender and the resulting material sieved through a 1 mm mesh. This method resulted in the preparation of PDMS particles, which were then surgically implanted into the test animals through an incision using a syringe. Control animals were sham-treated (i.e., they were surgically manipulated in the same manner as the treated animals). A total of 1 gram of shell particles or silicone elastomer dispersion particles or 4 grams of responsive silicone gel were implanted per animal. Following implantation, the animals were observed for clinical signs of toxicity twice daily and palpated for tumors weekly; body weights were recorded weekly. Clinical chemistry and hematology were assessed prior to implantation, at the time of interim sacrifices (3 and 12 months), and at study termination (24 months). At the interim and final sacrifices, the liver, heart, kidneys, spleen, brain and adrenal glands were weighed. Additionally, histopathology was done on the lung, liver, kidneys, heart, mammary glands, lymph nodes, spleen, implantation site and any gross lesions.

No effects on clinical signs, body weights, hematology, clinical chemistry, or organ weights were observed in treated groups. Histopathologic findings were limited to implantation site-related sarcomas in all treated groups. These findings were characterized by progressive fibrosis, collagen formation, inflammation, mineralization and brown pigment deposits. Because these findings of solid-state carcinogenesis are considered rodent-specific and not a risk for humans, the dose of PMDS particles applied in this study was considered a NOAEL for chronic toxicity and used to derive a NSRL.

The animals weighed 140-190 grams at the time of implantation. Using an average body weight value of 165 grams, the 1 g dose is converted to 6.06 g/kg body weight. Applying a 10-fold safety factor for extrapolating from rats to humans and another 10-fold safety factor to account for human variability, a NSRL of 0.0606 g/kg is determined. Assuming a woman's average body weight is 60 kg, this translates to a total allowable exposure of 3.64 g/person.

Potential Dose of PDMS Particles from SILIMED Implants

Total potential doses of PDMS particles from the SILIMED breast implants were determined based on the particle counts reported in the TÜV report. These calculations are shown in Table 1. In the TÜV report, the particles were classified according to size as either >20 µm or <20 µm and the number of particles per cm^2 surface area reported. For each size category, the volume of particles per cm^2 surface

area was calculated assuming that the particles were perfect spheres[2] and had a diameter of either 20 µm (for particles <20 µm) or 100 µm (for particles >20 µm). These assumptions maximize the total possible particle volume. These volumes were then converted to gram weights based on a specific gravity of 1.1 grams per cm^3 (SILIMED, personal communication). Based on a maximum implant surface area of 588 cm^2 (SILIMED, personal communication), the total dose of PDMS particles to a woman with two implants was then calculated. The resulting total doses of PDMS particles were found to be 48- to 1721-fold lower than the NSRL value calculated based on the highest (only) dose tested in the 24-month rat study.

Total doses of PDMS particles from the SILIMED breast implants were also determined based on the particle counts reported in the SILIMED report. These calculations are shown in Table 2. It should be noted that the methods used for quantifying particles for the SILIMED report involved direct examination of the implants, which does not allow for the distinction between surface particles and embedded particles (SILIMED, personal communication). Thus, the numbers of particles observed was considerably greater than reported in the TÜV report. However, the vast majority of these particles (51.8-97%) were classified as being under 10 µm, a size that would be difficult to observe at the magnification level used in the TÜV study. Additionally, it is likely that many of the particles observed in the SILIMED investigation are embedded in the implant material and thus, not readily available to the patient. In the SILIMED report, the particles were classified into 4 different size categories: ≤10 µm, 10-20 µm, 20-50 µm, and 50-100 µm. The percentage of total particles per mm^2 surface area in each of these size categories was reported (SILIMED report, Table 2) as was the total number of particles per mm^2 and the total number of particles per mm^2 in the top two size categories (SILIMED report, Table 3). To determine the total number of particles in the two smaller size categories, the total particles per mm^2

[2] Volume of a sphere = $4/3 * \pi r^3$

Table 1. Total potential doses of PDMS particles from the SILIMED breast implants and margins of exposure based on the particle counts reported in the TÜV report.

	Particles >20 µm			Particles >20 µm			Total exposure assuming 2 implants/patient		
Implant #	#/cm^2	#/implant[a]	Volume (cm^3)/implant[b]	#/cm^2	#/implant[a]	Volume (cm^3)/implant[c]	cm^3	grams	Margin of exposure
1	26	14,508	0.00759	120	66,960	0.00028	0.0157	0.0173	209.9
2	28	15,624	0.00818	156	87,048	0.00036	0.0171	0.0188	193.5
3	18	10,044	0.00526	144	80,352	0.00034	0.0112	0.0123	295.5
4	115	64,170	0.03358	279	155,682	0.00065	0.0685	0.0753	48.3
5	17	9,486	0.00496	160	89,280	0.00037	0.0107	0.0117	309.6
6	22	12,276	0.00642	90	50,220	0.00021	0.0133	0.0146	249.1
7	12	6,696	0.00350	123	68,634	0.00029	0.0076	0.0083	435.9
8	7	3,906	0.00204	55	30,690	0.00013	0.0043	0.0048	760.8
9	5	2,790	0.00146	42	23,436	0.00010	0.0031	0.0034	1060.8
10	10	5,580	0.00292	56	31,248	0.00013	0.0061	0.0067	541.7
11	5	2,790	0.00146	50	27,900	0.00012	0.0032	0.0035	1048.2
12	3	1,674	0.00088	36	20,088	0.00008	0.0019	0.0021	1721.5

[a] Assuming total surface area of 558 cm^2 (client communication).

[b] Assuming all particles >20 µm are perfect spheres of 100 µm diameter.

[c] Assuming all particles <20 µm are perfect spheres of 20 µm diameter.

Table 2. Total doses of PDMS particles from the SILIMED breast implants and margins of exposure based on the particle counts reported in the SILIMED report.

Implant #	Particles ≤10 µm		Particles 10-20 µm		Particles 20-50 µm		Particles 50-100 µm		Total particle volume (cm^3)/ mm^2	Total exposure assuming 2 implants/patient		Margin of exposure
	#/mm^{2a}	Volume (cm^3)/mm^{3b}	#/mm^{2c}	Volume (cm^3)/mm^{3d}	#/mm^2	Volume (cm^3)/mm^{3e}	#/mm^2	Volume (cm^3)/mm^{3f}		cm^3	grams	
5604622	2483	1.3×10^{-06}	59	2.5×10^{-07}	8	5.2×10^{-07}	6	3.1×10^{-06}	5.21×10^{-06}	0.581	0.640	5.7
5726746	1162	6.1×10^{-07}	115	4.8×10^{-07}	28	1.8×10^{-06}	5	2.6×10^{-06}	5.54×10^{-06}	0.618	0.680	5.3
5729883	180	9.4×10^{-08}	58	2.4×10^{-07}	3	2.0×10^{-07}	1	5.2×10^{-07}	1.06×10^{-06}	0.118	0.130	28.0
5736201	381	2.0×10^{-07}	50	2.1×10^{-07}	2	1.3×10^{-07}	1	5.2×10^{-07}	1.06×10^{-06}	0.118	0.130	27.9
5736209	545	2.9×10^{-07}	177	7.4×10^{-07}	9	5.9×10^{-07}	4	2.1×10^{-06}	3.71×10^{-06}	0.414	0.455	8.0
5799314	269	1.4×10^{-07}	90	3.8×10^{-07}	51	3.3×10^{-06}	23	1.2×10^{-05}	1.59×10^{-05}	1.773	1.951	1.9
5799315	97	5.1×10^{-08}	32	1.4×10^{-07}	56	3.7×10^{-06}	2	1.0×10^{-06}	4.90×10^{-06}	0.546	0.601	6.0
5799316	461	2.4×10^{-07}	266	1.1×10^{-06}	26	1.7×10^{-06}	8	4.2×10^{-06}	7.24×10^{-06}	0.808	0.889	4.1
5799317	377	2.0×10^{-07}	105	4.4×10^{-07}	88	5.8×10^{-06}	4	2.1×10^{-06}	8.49×10^{-06}	0.947	1.042	3.5
5829057	98	5.1×10^{-08}	18	7.6×10^{-08}	7	4.6×10^{-07}	1	5.2×10^{-07}	1.11×10^{-06}	0.124	0.136	26.7

[a] Calculated based on percent of particles in the ≤10 µm size bin and the average number of particles/mm^2 reported in SILIMED study (SILIMED, 2015).

[b] Assuming all particles ≤10 µm are perfect spheres of 10 µm diameter.

[c] Calculated based on percent of particles in the 10-20 µm size bin and the average number of particles/mm^2 reported in SILIMED study (SILIMED, 2015).

[d] Assuming all particles 10-20 µm are perfect spheres of 20 µm diameter.

[e] Assuming all particles 20-50 µm are perfect spheres of 50 µm diameter.

[f] Assuming all particles 50-100 µm are perfect spheres of 100 µm diameter.

was multiplied by the percentage of particles in each of these size categories. For each size category, the volume of particles per mm^2 surface area was calculated assuming that the particles were perfect spheres and had the following diameters: 10 µm (for particles <10 µm), 20 µm (for particles 10-20 µm), 50 µm (for particles 20-50 µm), or 100 µm (for particles 50-100 µm). These assumptions maximize the total possible particle volume. The volumes were then converted to total gram weights based on a specific gravity of 1.1 grams per cm^3, a maximum implant surface area of 588 cm^2 (58800 mm^2), and an assumption of two implants per woman. The resulting total doses of PDMS particles were found to be substantially higher than those calculated based on the TÜV report, but were still 1.8- to 28-fold lower than the NSRL value calculated based on the 24-month rat study.

This assessment shows that, based on the total numbers of particles reported in both the TÜV and SILIMED investigations, the total PDMS particle dose associated with the SILIMED breast implants is below the NSRL. It should be noted that these calculations are relatively conservative in that they assume that all of the particles counted on the breast implants are on the surface on the device and are bioavailable. However, regarding the SILIMED analysis many of the particles may actually be embedded into or attached to the implant shell, and thus, are not bioavailable. Even those particles that are not embedded into the shell may remain adhered to the surface and become encapsulated with the device once it is implanted subcutaneously.

Several conservative assumptions have been incorporated into the derivation of the margins of exposure for particle counts that likely overestimate the potential exposure and therefore overestimate the risk to patients. For example, it is assumed that the particles are spherical in shape and that all particles have a diameter that represents the maximum value for that particle size bin. In addition, a maximum silicone breast implant surface area was assumed and a female body weight between the 15th and 25th percentile (EPA 2011). It was also assumed that all particles observed in the SILIMED investigation were loose on the surface of the implant and thus, available to the patient, although this is unlikely to have been the case. Furthermore, a 100-fold safety factor was used in derivation of the NSRL value. Collectively, the conservative nature of these assumptions is compounded in the risk assessment approach, resulting in cautious estimates of risk that are protective of patients' health.

Fibers – Glass, Textile and Other

No Significant Risk Level (NSRL) for Fibers

Regulatory levels for exposure to glass and other synthetic vitreous fibers are available from both the National Institute for Occupational Health and Safety (NIOSH, 2011) and the American Conference of Governmental Industrial Hygienists (ACGIH, 2001). These exposure limits were established for the protection of workers from the potential adverse effects associated with inhalational exposures. With inhalation exposure, only fibers that are small enough to be respired can be deposited in the lung and cause potential toxicity. Further, macrophages in the lung tend to be more active in clearing fibers than those in muscle or subcutaneous tissue, which may contribute to greater biopersistence of fibers when implanted in the body than when they are inhaled. Nevertheless, the general mechanisms involved in causing injury are the same via inhalation as with subcutaneous exposure.

The recommended exposure limit (REL) established by NIOSH is a time-weighted average (TWA) for a 10-hour work day and equates to 3 fibers per cm^3 of air. The permissible exposure limit (PEL) established by ACGIH is a TWA for an 8-hour work day and equated to 1 fiber per cm^3 of air. These exposure limits are derived using uncertainty factors to provide a reasonable certainty of no harm. Thus, these factors support a conclusion of extremely low risk or very high margins of exposure. The NIOSH and ACGIH exposure limits were converted to lifetime fiber burdens based on:

1. The inhalation rate during moderate activity for an average adult 2.1 m^3 per hour, as provided in the U.S. EPA exposure factors handbook (EPA, 2011);
2. Either a 10-hour work shift (for the NIOSH exposure limit) or an 8-hour work shift (for the ACGIH exposure limit);
3. Exposure for 5 days/week, 52 weeks/year, and a 30-year occupational lifetime;
4. An estimated airway surface area of 62.7 m^2; and
5. An estimated lung deposition rate of approximately 5% (Fayerweather et al., 1997).

Based on these calculations, the NIOSH REL and ACGIH PEL equate to lifetime fiber burdens of 39,186 fibers and 10,450 fibers, respectively.

Potential Dose of Fibers from SILIMED Implants

In the TÜV report, the number of total glass fibers identified on the areas of the implants sampled ranged from 1-6 (TÜV, 2015); the total surface area surveyed was not reported. In addition to these glass fibers, curled fibers, straight fibers, and textile fibers were quantified on a per cm^2 surface area (TÜV report, Table 5); these are totaled in Table 3 and range from 2.4 to 9.4 fibers per cm^2. The specific identity of these fibers, however, was not provided. When compared to the lifetime fiber burden of 39,186 fibers based on the NIOSH REL, the numbers of fibers associated with the implants provide margins of exposure ranging from 4169 to 16,328. When compared to the lifetime fiber burden of 10,450 fibers based on the ACGIH PEL, the numbers of fibers associated with the implants provide margins of exposure ranging from 1112 to 4354.

In the SILIMED report, the particles including fibers were classified according to morphology. The percentage of total particles per mm^2 surface area that were classified as fibers was reported (SILIMED report, Table 1) as was the total number of particles per mm^2 (SILIMED report, Table 3). These values were used to calculate the number of fibers/cm^2 surface area (Table 4). It should be noted that the methods used for quantifying particles for the SILIMED report involved direct examination of the implants, which does not allow for the distinction between surface particles and embedded particles and it is likely that many of the particles observed were embedded in or attached to the implant material and thus, are not readily available to the patient. When compared to the lifetime fiber burden of 39,186 fibers based on the NIOSH REL, the numbers of fibers associated with the implants provide margins of exposure ranging from 15 to 608. When compared to the lifetime fiber burden of 10,450 fibers based on the ACGIH PEL, the numbers of fibers associated with the implants provide margins of exposure ranging from 4 to 162.

Table 3. Total number of fibers per cm^2 surface area and margins of exposure based on fiber numbers reported in the TÜV report.

	Number of fibers/cm^2				Margins of Exposure	
Implant #	Curled	Straight	Textile	Total	Based on NIOSH REL	Based on ACGIH PEL
1	3	1	1.1	5.1	7684	2049
2	1	2	1.2	4.2	9330	2488
3	2	3	2.4	7.4	5295	1412
4	2	4	2.1	8.1	4838	1290
5	3	4	2.4	9.4	4169	1112
6	3	2	2	7	5598	1493
7	2	1	1.6	4.6	8519	2272
8	2	2	1.3	5.3	7394	1972
9	1	1	0.4	2.4	16,328	4354
10	0	2	0.8	2.8	13,995	3732
11	1	1	0.6	2.6	15,072	4019
12	1	2	1	4	9797	2612

Table 4. Total number of fibers per cm^2 surface area and margins of exposure based on fiber numbers reported in the SILIMED report.

				Margins of Exposure	
Implant #	# particles/mm^2	% fibers	# fibers/cm^2	Based on NIOSH REL	Based on ACGIH PEL
5604622	2560	1	2560	15.3	4.1
5726746	1321	1	1321	29.7	7.9
5729883	243	0.5	121.5	322.5	86.0
5736201	432	1	432	90.7	24.2
5736209	737	1	737	53.2	14.2
5799314	372	0.5	186	210.7	56.2
5799315	188	0.5	94	416.9	111.2
5799316	764	0.5	382	102.6	27.4
5799317	575	0.5	287.5	136.3	36.3
5829057	129	0.5	64.5	607.5	162.0

This assessment shows that, based on the total numbers of fibers reported in the TÜV and SILIMED investigations, the total fiber dose associated with the SILIMED breast implants is well below the NIOSH REL and ACGIH REL.

Several conservative assumptions have been incorporated into the derivation of the margins of exposure for fiber counts that likely overestimate the potential risk to patients. For example, the fiber counts on the breast implants are assumed to be comparable to respirable fibers, which tend to be of a small size. Larger fibers are more likely to be encapsulated with the implant and not be bioavailable. It

was also assumed that all fibers observed in the SILIMED investigation were loose on the surface of the implant and thus, available to the patient, although this is unlikely to have been the case. In addition, the REL/PEL values already include uncertainty factors to reflect a reasonable certainty of no harm. These factors support a conclusion of extremely low risk or very high margins of exposure. Collectively, the conservative nature of these assumptions is compounded in the risk assessment approach, resulting in cautious estimates of risk that are protective of patient health.

Silver

In the TÜV study, a single particle of silver was observed on one of the implants. Similar particles on other implants were not reported. Nevertheless, SILIMED requested that a risk assessment be conducted based on this single particle.

No Significant Risk Level (NSRL) for Silver

The U.S. Environmental Protection Agency (EPA) has established an oral reference dose (RfD) for silver based on results of a human intravenous (i.v.) study, in which silver arsphenamine was administered in divided doses over a period of two or more years (EPA, 1991). The oral RfD itself is not appropriate for assessing the potential risk of implanted material, but the underlying study can be used to derive an NSRL. This same study also served as the basis for the International Conference on Harmonisation (ICH) derivation of a daily permissible exposure level for silver in drug products (ICH, 2014). The minimal effect level from this study was determined to be 1 gram of metallic silver based on the lowest i.v. dose of silver arsphenamine (4 grams; 23% silver) resulting in argyria in one patient. Applying a 10-fold safety factor for extrapolating from the lowest-observed-effect-level (LOEL) to a no–observed-effect-level (NOEL) and another 10-fold safety factor to account for human variability, a NSRL of 10 mg is calculated.

Potential Dose of Silver Particle from SILIMED Implants

The particle of silver was reported to be 1.57 mm in length and 0.4 mm in width. The thickness of the particle was not reported. Therefore, based on the photomicrograph of the particle (Figure 29 of the TÜV report), the particle was assumed to be as thick as it was wide (0.4 mm). Assuming a rectangular shape, the volume of the particle was then calculated to be 0.25 mm^3. Based on a density for silver of 10.49 g/cm^3 (ATSDR, 1990), the total mass of silver in the particle was calculated to be 2.63 mg. This dose of silver as presented in Table 5, is approximately 3.8-fold lower than the NSRL value calculated based on the human i.v. study.

Table 5. Total dose of silver in mg and margin of exposure based on dimensions of the silver particle reported in the TÜV report.

Particle volume (mm^3)[a]	Particle weight (mg)	Margin of exposure
0.2512	2.64	3.79

[a] Based on the assumption that the particle is as thick as it is wide and that it is rectangular in shape.

This assessment shows that dose of silver associated with the single particle observed in the TÜV report is below the NSRL and should not be associated with a risk to health.

Several conservative assumptions have been incorporated into the derivation of the margin of exposure for the silver particle that likely overestimate the potential risk to patients. It is assumed that the particle is as thick as it is wide, maximizing the size of the particle. Furthermore, not all of the silver ions present in this single particle would be bioavailable at one time; only the silver ions on the outside surface of the particle would be accessible, representing limited exposure over time. Collectively, the conservative nature of these assumptions is compounded in the risk assessment approach, resulting in estimates of risk that are protective of patient health.

CONCLUSIONS

At the request of SILIMED, Exponent has conducted a review of the toxicity and an assessment of the solid foreign material detected on SILIMED's silicone breast implants to evaluate the potential clinical impact to the patient receiving these breast implants. Three separate types of materials have been detected on the implants: particles (assumed to be polydimethylsiloxanes), glass and textile fibers, and silver. Based on various optical evaluations, RMS/TÜV and SILIMED determined the surface concentration of solid foreign material on numerous sample breast implants. Based on these analytical findings and the toxicity of the various materials, Exponent conducted a risk assessment of these materials that included the derivation of margins of exposure for patients potentially exposed to the foreign material on the implants. Each of these margins of exposure incorporates at least a 100-fold safety factor; therefore, a margin of exposure of one or higher is protective of human health.

The margins of exposure for dislodgeable particles as quantified by TÜV range between 48 and 1721. SILIMED conducted their analysis based on a quantification of all particles on the surface of the implant; this method does not distinguish between dislodgeable and embedded particles, which resulted in higher particle counts. The margins of exposure for all particles from the SILIMED analysis ranged from 2 to 28. Thus, the margins of exposure for particles for all samples are greater than one.

The margins of exposure for dislodgeable fibers as quantified by TÜV range between 1112 and 4354. As noted above, SILIMED counted all fibers with the margins of exposure for all fibers ranging from 4 to 162. Thus, the margins of exposure for fibers for all samples are greater than one.

A single silver particle was detected in the TÜV analysis. The margin of exposure for the silver particle is 4.

Exponent's risk assessment of the solid foreign materials observed on SILIMED's breast implants was conducted in a standard and conservative manner. Several factors contribute to the conservative nature of the provided margins of exposure. Many of the exposure assumptions are upper bound and represent a reasonable worst case, including the use of the maximum size breast implant and the body weight of a small woman (15^{th} to 25^{th} percentile). A maximum size was assumed for all particles, including the silver particle. The maximum size incorporated use of a spheroid shape for the volume of the particle as well as use of the largest diameter possible for each particle size bin. It is also assumed that these particles and fibers are all bioavailable. Finally, a safety factor of at least 100-fold has been applied to the derivation of the NSRLs.

As evidenced by the calculated margins of exposure, the presence of particles, textile or glass fibers, and silver on the surface of the SILIMED breast implants at the quantities reported in the TÜV and SILIMED analyses do not pose an unacceptable risk to a patient from the implantation of SLIMED's silicone breast implants.

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