Scientific Committee on Emerging and Newly Identified Health Risks

SCENIHR

Opinion on

The safety of Poly Implant Prothèse (PIP) Silicone Breast Implants
Update of the Opinion of February 2012

SCENIHR approved this opinion by written procedure on 12th of May 2014

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ABSTRACT

PIP silicone gel filled breast implants (PIP implants) are reported to have a higher prevalence and incidence of implant ruptures than other silicone breast implants, and ruptures also tend to occur earlier in the implant life than is the case with other implants. These reports indicate that the shell/patch or the manufacturing process for a number of batches of PIP implants was of inferior quality, which may be a reflection of variations in the manufacturing process. The risk of implant rupture increases with implantation time. Quantifying the actual increase in failure rate is problematic because the failure rates of non-PIP implants are not well documented.

The purpose of this Opinion is to update the previous SCENIHR opinion on PIP breast implants in February 2012, based on additional data which have become available since then.

In the previous opinion the effects of both released polymeric and unpolymerised silicones in general were considered. Since then several cyclic siloxanes (known as D4, D5 and D6) have been identified in PIP devices at higher concentrations than in other silicone breast implants. This has led to investigate the possible toxicological consequences of cyclic siloxanes release from damaged PIP implants. It has become apparent that these chemicals are commonly present in the bodies of women even without breast implants. This is a consequence of the widespread use of siloxanes in many domestic products. Cyclic siloxanes D4, D5 and D6 are non-toxic and not irritant in standard tests.

In some cases, implant gel-bleed or rupture has been associated with an inflammatory reaction either locally or in regional lymph nodes. In other cases, ruptures were free of symptoms. There is no new evidence on the reasons for this variation in the response of individual recipients. Neither implant rupture, nor local inflammation, has been found to be associated with breast cancer or anaplastic large cell lymphoma. While there are differences in rupture rates, there is no reliable evidence that ruptured PIP implants create a greater health risk than a ruptured silicone breast implant from another manufacturer.

In the case of implant rupture, explantation is advised. Because of the widespread concern of undetected ruptures, there is a need for women with PIP breast implants to seek regular clinical examinations, and where deemed appropriate, individual counselling and imaging with ultrasonography or MRI.

There is currently no convincing medical, toxicological or other data to justify routine removal of intact PIP implants. Implant removal in the absence of malfunction may be considered for women who are experiencing significant anxiety because they have a PIP breast implant. However, the decision to remove an intact PIP implant for this reason should be based on an individual assessment of the woman's condition by her surgeon or other treating physician after consultation.

Keywords: SCENIHR, PIP breast implants, implant failure, safety evaluation, toxicity, silicone

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1. EXECUTIVE SUMMARY

This update of the Opinion of February 2012 is based on four sources of data, namely:

- An extensive search of the literature published since the last opinion in February 2012;
- The responses to a questionnaire devised by the Committee and sent out in November 2012;
- Information provided by Member States (i.e. UK, France, Spain, Sweden) and Australia;
- Incident reports collected by the IPRAS (International Confederation for Plastic Reconstructive and Aesthetic Surgery) network.

1.1. Incidence of implant failures

There is no indication from the available data that the demographic profile of women who have had PIP silicone gel filled breast implants (PIP implants) differ from women with implants from other manufacturers.

Silicone breast implants may fail, regardless of manufacturer. The probability of rupture for PIP implants is estimated to be around 25-30% at 10 years after implantation, while other silicone breast implants have been reported with a rupture rate of 2-15% after 10 years of implantation. Although the incidence of PIP implant ruptures is reported to be higher than of those of other silicone breast implants, the available data on non-PIP implant failures is quite heterogeneous and it is therefore not possible to make a precise estimate on the excessive failure rate of PIP implants.

In addition ruptures of PIP implants are reported to occur earlier in the implant life than for other implants.

The main factors that contribute to breast implant failure are:

- The chemical, physical and mechanical properties of both the gel filling and the shell of the implant;
- The quality of the surgical procedure for implantation;
- The ageing of materials following implantation.

The reason for the higher failure rate of PIP implants appears to be that the shell/patch or other parts of the implant for a large number of batches of PIP implants were of inferior quality. This may reflect considerable variability in the manufacturing process.

1.2. Chemical composition of PIP implants

Silicone based breast implants, regardless of manufacturer, contain low molecular weight siloxanes. PIP devices have recently been found to contain higher amounts of certain cyclic siloxanes than those of other breast implants, namely D4 (octamethylcyclotetrasiloxane), D5 (decamethylpentasiloxane) and D6 (dodecamethylcyclohexasiloxane). The analysis of PIP implants has failed to detect any

other significant differences in composition compared to silicone breast implants of other manufacturers.

Thus the questions arise, whether the higher levels of these cyclic siloxanes in the PIP implants could contribute to the higher failure rate and whether the release of these siloxanes, in case of implant leakage or rupture, could have adverse health consequences for patients.

1.3. Exposure considerations

Evidence shows that, even in women without breast implants, siloxanes can be detected in various organs due to exposure to siloxanes in cosmetics and other household products. Consequently, nursing women, regardless of whether or not they have breast implants, are likely to have detectable levels of siloxanes in their breast milk.

Following implant rupture, released siloxanes such as D4, D5 and D6 are likely to either be cleared from the blood and lymph over time or, because of their lipophilic nature, to be deposited in fatty tissues. Their metabolites have enhanced water solubility, which makes the urine the principal excretion route.

1.4. Toxicological properties

Laboratory tests on PIP implants have been negative for cytotoxicity and genotoxicity. However one study (discussed in the 2012 SCENIHR Opinion on PIP breast implants) reported a "mild irritancy potential on animals not present in gels from other manufacturers"; but, in spite of repeated attempts this result has not been reproduced since. PIP implants have also been subjected to chemical analysis in an effort to find organic and inorganic compounds (including heavy metals) that may be potentially toxic, but none have been found even at very low levels.

Regarding implant composition, in relation to possible toxicity, the main difference between PIP implant gels and gels used in other silicone breast implants is the higher concentrations of the cyclic siloxanes such as D4, D5 and D6.

To ascertain possible adverse health consequences for patients, of the release of cyclic siloxanes from a PIP implant, a thorough review of the toxicological properties of D4, D5 and D6 has been carried out. The conclusion is that these compounds are of low toxicity after both acute and chronic exposure. They are also not genotoxic or irritant. Significant adverse effects were found only in animals at high exposure levels that are considered not to be relevant for human health.

Thus, the health effects resulting from exposure to PIP breast implant silicone are unlikely to differ from those associated with implant silicones used by other manufacturers.

Although there are siloxanes other than D4 D5 and D6 present in breast implants, there is no reason to assume that their toxicological properties would differ significantly from those of D4, D5 and D6.

1.5. Consequences of implant failure

A leaking or ruptured implant does not necessarily result in adverse effects either immediate or longer term. However, free silicone and/or gel-bleed can cause siliconomas, lymphadenopathy, lumps etc. This has been discussed in the previous Opinion. These effects have been reported less frequently for bleeds than implant ruptures.

PIP implants have not been associated with higher risks of clinical problems such as haematoma, capsular contracture or cancer. In the French ANSM report on 30,000 women with PIP implants 16.8% encountered failure of at least one of their implants and 9% at least one adverse effect. These figures are somewhat lower in other studies. Some cases of implant gel-bleed or rupture are associated with an inflammatory reaction locally or in the regional lymph nodes. There is no new information to explain this inter-subject variability.

There is conflicting evidence regarding whether there are more women with PIP implants who have experienced signs of loco-regional inflammation compared with women with other silicone breast implants. There is no convincing evidence that the risk of adverse effects after rupture of PIP- implants is higher than the risk after rupture of other silicone breast implants. Nonetheless the overall risk of adverse effects is higher for PIP-implants due to the higher risk of rupture.

Although the total number of case reports on Anaplastic Large Cell Lymphoma (ALCL) increased substantially in 2012, the evidence is insufficient to attribute this to PIP implants.

There is evidence showing that concerns about PIP breast implants have had a marked psychological impact on a number of patients.

1.6. Generic Risks and Benefits of removal of PIP silicone breast implants

From a public health perspective it is important to identify generic risks and benefits. However, such a generic assessment may not necessarily apply to each patient who needs to be evaluated on an individual basis.

In view of the high rupture rates, many women having PIP breast implants can be expected within their lifetime to experience ruptured implants.

There is inevitably a higher intra- and postoperative risk associated with the removal of ruptured implants than with intact implants. After removal, new implants cannot be inserted immediately if the patient has significant inflammation at the explant site. In case of implant failure and/or in the presence of loco-regional inflammation or lymphadenopathy, there is general agreement among plastic surgeons that explantation is needed. There is currently no convincing medical, toxicological or other data to justify the routine removal of intact PIP implants. Implant removal in the absence of malfunction may be considered for women who are experiencing significant anxiety because they have a PIP breast implant. However, the decision to remove an intact PIP implant for this reason should be based on an individual assessment of the woman's condition by her surgeon or other treating physician after consultation.

1.7. Recommendations for further work

Although breast implants are the most commonly used devices containing silicones, SCENIHR is aware of the fact that problems might be encountered also with other silicone implants such as body building (muscle) implants or buttock implants, however, as yet, there are almost no data available for such implants.

The SCENIHR identifies the need for:

a) Information to breast implants recipients

The SCENIHR stresses the importance that recipients of breast implants are informed of possible risks, including that of device failure, which increases with time. Therefore, a

significant percentage of women can be expected to experience a ruptured implant within their life span.

b) Improved data on for breast implants

Implementation of a registration system of breast implantations on a national or European level is of utmost importance for collecting and analyzing data for research and risk assessment purposes. The questionnaire developed for this opinion could provide a valuable tool for this purpose. There is still a need for better reporting of breast implant failures, in particular of ruptures, through the mandatory vigilance reporting system to identify potential design problems earlier.

c) Explant analysis

A retrieval study, focusing on an adequate sample of explanted devices, would enable identification of causes of implant failures, rupture mechanism, and individual body-device interaction for better understanding and safer device design.

d) Information on factors causing inflammation

A better understanding of the causes of the local inflammation/irritancy is needed. This includes the impact of the device/tissue interface of the shell on the development and characteristics of the tissue capsule.

e) Future clinical examinations

Women with silicone breast implants have a need for regular screening for potential leakage. Currently the most accurate mode of detecting ruptures is by medical imaging, namely Magnetic Resonance Imaging (MRI). There is a need for low cost reliable diagnostic methods, suitable for routine use, to identify implant status (leakage, rupture) in patients. It is also important to improve the understanding of inter-individual differences in vulnerability to the effects of a leaking/ruptured implant since the available data indicate substantial variations.

f) Qualification of practitioners

Although the SCENIHR has been unable to investigate the impact of poor surgery on implant failure it is concerned that implant operations may be carried out by individuals who are poorly qualified/experienced to conduct breast implantations.

2. BACKGROUND

The company Poly Implant Prothèse produced silicone gel filled breast implants (PIP implants) in their latest available form since 2001. These implants have been found to contain silicone that had not been certified to be suitable for use in implants and had not been produced according to the legal requirements to achieve CE marking. Devices have been available in smooth and textured variants. If classified by the date of production, they could be considered as third or fourth generation PIP implants. However, based on reports of a large number of early ruptures, as well as heavy gel bleeds, these implants behave like the older and inferior second generation implants. (See Appendix II) In addition to the brand name 'PIP' such implants have also been marketed by other companies under the brand name 'M-implants', 'Rofil implant' and 'TiBreeze'.

Following the scientific opinion 'The Safety of PIP Silicone Breast Implants', adopted by SCENIHR in February 2012, additional data and further evidence became available, thus requiring it to be updated.

The update of the opinion is based on additional data, which have been produced by and collected from the Member States and other international fora, such as the International Laboratory Testing Panel for PIP breast implants[1], in 2012 and 2013. Efforts to produce this data are still on-going.

The data comprise:

- the physical and chemical properties of the gel and of the envelope/shell;
- the toxicological properties;
- the incident reports and any other relevant data on the implanted patients follow-up.

In order to collect sufficient, relevant data two sorts of activities were envisaged.

1. The development of an EU questionnaire on implanted patients, to be distributed at national level. An EU questionnaire was developed based on available models from the Member States and used to collect data on women with breast implants.

2. Available and forthcoming scientific information on PIP silicone breast implants were collected. If available, besides the data produced by the clinical trials, additional literature published in the meantime was taken into account.

[1] Established by the Australian Therapeutics Good Administration, with international participation. http://www.tga.gov.au/safety/alerts-device-breast-implants-pip-120224.htm

3. TERMS OF REFERENCE

In the light of the above considerations, the SCENIHR is requested to provide an updated scientific opinion on 'The safety of PIP silicone breast implants'.

In particular, the SCENIHR is asked:

1. To contribute to the creation of an EU questionnaire to be used for the collection of data on implanted patients;

2. To provide guidance on the testing undertaken by the Member States in terms of tests and studies to be performed, test methodologies, uniform data production;

3. To collect, compile and analyse the data collected;

4. To update its scientific opinion on the safety of the PIP silicone breast implants.

4. APPROACH USED TO DEVELOP THIS OPINION

4.1. Summary of the previous opinion

The previous opinion was established in response to an urgent request from the Commission Services. As the present Opinion is an update, the key conclusions from the initial opinion (SCENIHR 2012) are summarized below in section 4.1.1 to 4.1.4 (included).

4.1.1. Recipients of implants

There is no indication from the available data that the women who have had PIP implants differ significantly in important respects from the group of women having implants from other manufacturers. Overall around 80% of all breast implantations are performed for cosmetic reasons and about 20% for reconstructive purposes. A minor fraction of implantations involve women with congenital malformations.

4.1.2. Reasons for breast implant failure

The risk factors for breast implant failure were identified as:

- Physical and chemical features of the initial implant;
- The implantation procedure and site;
- Time since the implantation and associated material degradation;
- Personal-specific factors such as lifestyle, sportive activities or accidental mechanical overexposure.

4.1.3. Measurement of implant failures

There is international agreement among professional radiologists and reconstructive and aesthetic surgeons that Magnetic Resonance Imaging (MRI) is the most accurate available modality to detect ruptures. A meta-analysis has estimated the overall sensitivity as being 78% (95% CI, 71%-83%) and the overall specificity was 91% (95% CI, 86%- 94%). Ultrasonography is the second best diagnostic modality for detecting ruptures. However, ultrasonography is less precise and more dependent on the human operator than MRI. X-ray mammography is even less useful.

4.1.4. Possible adverse health consequences

Capsular contracture has been reported the most frequent reason for additional surgery in women with breast implants with fractions ranging from 2% to 23%. Clinically, capsular contracture is classified according to the Baker classification scheme with no or slight contracture as I and II, more substantial and serious contracture, respectively, as III and IV, with additional dislocation in IV. Apart from aesthetic consequences, Baker III and IV contracture may cause persisting pain.

Possible health effects of silicone breast implants that have been investigated in epidemiological studies include:

a) Lymphoma: A causal link between breast implants and lymphoma has not been established.

ALCL: A very rare type of lymphoma, the Anaplastic Large Cell Lymphoma (ALCL) has been found in the scar capsular tissue around breast implants, globally, 130 cases have been reported so far.

b) Breast cancer and other cancers: Several high-quality studies have been conducted and they have provided clear evidence against an increased risk of breast cancer or any other type of cancer. An increased risk of lung cancer found in some studies appears to reflect a higher frequency of smoking among women with implants.

c) Connective Tissue Diseases (CTDs): Although there were initial reports of associations with various forms of connective tissue disease, subsequent, large-scale epidemiologic investigations provided no evidence for these claims.

d) Effects on offspring: There were a few early case reports of children born or breastfed by women with silicone breast implants who developed swallowing difficulties, irritability, non-specific skin rashes, fatigue, and other symptoms. However, subsequent epidemiologic studies of these issues found no evidence of an association.

e) Immunological effects: adverse reactions have been reported in a small number of women with breast implants.

f) Suicide and psychological issues: It is a consistent observation that the population of women with breast implants for cosmetic reasons exhibits a two- to three-fold higher rate of suicide than similar-aged women in the general.

g) Infection rates rank low among the potential complications of breast reconstruction or breast augmentation. They could appear early or be detected as subclinical in the pathogenesis of fibrous contracture.

The causes of adverse effects were also addressed. Consideration was given both to the released polymeric material and to the release of siloxanes. Data on the identification and the consequently the relevant toxicology of the siloxanes was both limited and preliminary. The distribution of polymeric material and its effects were discussed.

4.2. Design and administration of the SCENIHR questionnaire

SCENIHR has developed a questionnaire (see appendix 1), primarily to identify whether there were differences between patients with PIP implants compared with those with other breast implants in:

i) the nature, frequency and/or severity of adverse effects prior to and at explantation and the correlation between these;
ii) the time to rupture and/or rupture frequency and/or nature and extent of rupture;
iii) the extent of correlation between i) and ii).

The challenges in the design were:

- to devise a suitable electronic form that is simple to complete and considered relevant by those using it;
- to consider the extent to which the questionnaire can be simplified without loss of the ability to address the questions identified as of major importance;
- to ensure that the questions are not ambiguous.

The intended target group was practicing plastic surgeons. They were contacted either by their professional organizations and/or via their Member State encouraging them to

complete the questionnaire that was available on the DG SANCO website. The professional organizations, which responded, were from many countries including those from outside the EU.

4.3. Data sources used to develop the current opinion

This opinion is based on four sources of data, namely:

- a literature review, particularly focused on papers published since the previous opinion;
- Reports produced by individual member states and other countries;
- Information gathered by the International Conference for Plastic Reconstructive and Aesthetic Surgery (IPRAS);
- Responses to the questionnaire devised by the Working Group.

4.3.1. Literature published since the last Opinion in February 2012

The literature search was carried out in two parts. The *first task* was to update the previous literature review (carried out up to the beginning of 2012), which was used to create the previous Opinion. Preliminary searches were conducted on PubMed using the same search terms; Silicone breast implants, PIP implants, and silicone implants as for the previous opinion. This gave the results seen in the table below.

Table 1: Results of the initial data search

Search term(s)	**Number of articles**
Silicone breast implants/devices	2,597
PIP implants/devices	948
Silicone implants/devices	6,883

The abstracts for these were scanned. Potentially relevant articles were identified and grouped as far as possible under the same topics as in the previous review. The headings used were:

- Cancer
- Composition
- Infection
- Inflammation
- Other effects
- PIP implants
- Rupture
- Papers related to non-breast use of implants.

The *second task* involved searches for more specific terms in conjunction with major terms. Again, preliminary searches were conducted on PubMed, and the results can be seen in the table below. These searches were limited to publications from 2000 onwards.

Table 2: Publications found by implant type and effects of concern

	Silicone breast implants	**PIP implants**	**Silicone breast devices**
Rofil implant	0	0	0
Anaplastic large cell lymphoma	22	1	20
M implant	11	0	8
TiBreeze[#]	0	0	0
Leakage	18	3	18
Siloxane	660	17	664
Body fluid	13	0	13
Protein	79	3	81
Bacteria	23	0	21
Sensitization	2	0	2
Heavy metal	15	1	14

[#] - this term does not appear in PubMed.

Considerable overlap was found between the results for the first and third major terms. Very few results related specifically to PIP, so in addition searches for "poly implant prothese" (2000 onwards) and "poly implant prosthesis" plus the specific terms (2000 onwards) were conducted, but these did not produce any additional papers.

The abstracts for these searches were scanned to identify papers of potential interest. For this part of the search, papers were considered of interest if the specific term used in the search was clearly relevant to, or the main focus of, the main part of the paper. For example, there were a large number of hits for siloxanes, but only a few, where siloxanes were an important part of the paper. For the others, it is assumed that the term siloxanes is used in a general way in relation to the make-up of the implant. A further search was carried out up to May 10th 2013 using MEDLINE. Additional papers were also found by members of the working group

A weight of evidence approach was used to identify those papers for which a full text was required and to evaluate the evidence (SCENIHR 2012).

4.3.2. Reports produced by individual Member States and other governments

Because of the political and other concerns regarding PIP implants, there have been major efforts in several countries to assess the health implications of implant leakage and implant rupture. Much of this important work is not yet published in scientific literature. As a consequence the SCENIHR has deviated from its normal practice of relying almost exclusively on the published literature. Of particular importance for this opinion was work carried out by the UK, French, Australian, Spanish, and Swedish health authorities.

4.3.3. Incident reports collected by the IPRAS (International Confederation for Plastic Reconstructive and Aesthetic Surgery) network)

The International Confederation for Plastic Reconstructive and Aesthetic Surgery IPRAS unifies 105 national plastic surgery societies. Through this network incident reports about increased rupture rates, as well as local and disseminated inflammation in patients with PIP implants, were obtained. Furthermore, data from a large series of PIP explantations, performed by a single plastic surgeon in Brazil, was also reviewed. Additional pre-existing national breast implant registry data, e.g. from Austria, was made available through IPRAS.

4.3.4. Variability in the quality of PIP implants

A major challenge in analysing data concerning PIP implants is that there appears to have been variations in the quality of the implants between different batches (see section 5). This variability in the quality of PIP implants could result in the observed variability of rupture rates and possibly the health impact of ruptures.

Another challenge in analysing data concerning PIP implants is that often the PIP implants which are referred to are not well characterized.

5. PHYSICOCHEMICAL PROPERTIES OF PIP IMPLANTS

A considerable amount of literature is available in the area of chemical and physical characterisation of PIP implant gels. Considerable research has been conducted on the mechanical properties of PIP implant shells in an effort to find an explanation for the seemingly higher rates of rupture being experienced with PIP implants compared to other breast implants. The current section reports the results of PIP implant physico-chemical characterisation studies that have been conducted recently.

5.1. How a silicone gel breast implant is manufactured

Silicone gel filled breast implants such as PIP implants consist of an outer shell filled with a gel. Both the shell and the gel are manufactured using the polymer poly-dimethylsiloxane, also known as silicone.

The shell is a thin membrane - approximately 0.8 mm thick – of silicone elastomer. The shell is composed of several layers. In some implants the inner layer is made of a type of silicone, which is less permeable to small molecules (no implant is totally impermeable). Sometimes the outer layer is textured. The shell is cured to form an elastomer with a high degree of cross-linking between the silicone molecules.

The gel filling is typically manufactured using a two-component silicone fluid. When combined in the presence of catalyst and heated (cured), the two components react with each other to form a lightly cross-linked gel. It is important to note that not all the silicone in silicone gel is bonded to the gel. A typical breast implant gel consists of approximately 10% of cross-linked material, "swollen" by viscous silicone fluid which is free to migrate within and out of the gel network (Marotta et al, 2002).

Implants with a less permeable inner shell layer seem to have advantages both from a chemical and physical point of view. The internal shell layer can be sufficiently different from the gel components so that the diffusion of components (in particular low molar mass components) through the shell is hindered. The more permeable external layers have better mechanical properties and, at the interface between the layers, a crack or tear (single fault) can be prevented from damaging the entire shell (mandatory redundant safety mean). Sufficient adhesion between the layers is crucial. Insufficient adhesion leads to abrasion resulting in a less resilient implant shell.

The silicones from which implants are made have to undergo a great deal of testing to demonstrate that they are biologically safe. Once they are certified by laboratory testing the manufacturer provides assurances that they are manufactured in the same way every time. In the case of PIP implants the manufacturer used silicone raw materials, which were not approved for such gels. This does not necessarily mean that the gels were of lower quality or "industrial grade" – it just means that the biocompatibility of the gels for use in implants had not been verified and hence, associated risks not excluded.

5.2. Properties of PIP implant shells

The overwhelming majority of the published test data, in particular those published by the Australian Department on Health and Ageing, Therapeutic Goods Administration (TGA) show that the mechanical properties of new PIP implant shells meet the requirements of applicable international standards. There are unpublished reports that the tensile strength properties differ significantly between "textured" and "micro-textured" PIP implants. (Schubert, Personal communication). The TGA did report on the mechanical properties of textured but not on micro-textured shells because that type of

PIP implant was never supplied in Australia, and therefore not available to the TGA for testing.

The TGA performed extensive mechanical testing on PIP shells – both smooth and textured, and was unable to confirm earlier French findings of a weaker implant shell/membrane performance. However, tests on explanted PIP shells conducted by the TGA showed that the tensile strength of the shell is significantly reduced. This confirms early research (Brandon et al, 2000 and Marotta et al 2002) on the effect of endogenous lipids and other body fluids on the materials from which breast implants are made. Such effects may influence the permeability of the shell as well as the potential for rupture.

A recent Swedish study (Strömberg et al 2012 & 2013) investigated PIP (ruptured and non-ruptured) and non-PIP implants using Field Emission Scanning Electron Microscopy (FE-SEM) and Fourier Transform Infrared (FTIR) techniques. It concluded that "The reason for the failure of the shell could not be established".

In a PIP implant retrieval study (Swarts et al, 2013) impact resistance tests were conducted on 18 explants. Two of the 18 specimens burst during the impact resistance tests which were carried out according to the procedure ISO 14607 (Annex E.2). Because it tests the whole implant, impact resistance is far more sensitive to variations in the quality of the shell than tensile strength (e.g. variations in thickness and flaws introduced during manufacture). However the requirements in ISO 14607 apply only to new, finished (sterile) breast implants. It is well established that the mechanical properties of breast implant shells reduce significantly once implanted. Therefore, the fact that some explants did not meet the impact resistance requirements on new implants is not an unexpected result. However, the requirements should provide a sufficient safety margin to account for degradation by ageing and biochemical interactions during the entire intended product lifetime.

It has been observed (TGA testing updates, ANSM 2013, Swarts et al 2013) that key properties such as shell thickness displayed significant variation within sample and between samples of PIP implants. This higher variability could partly explain higher early rupture rates of PIP implants.

5.3. The contents: Chemical composition and physical properties of PIP implant gels

All commercial breast implants contain low molecular weight silicones that are not cross-linked to the gel matrix. These low molecular weight silicone compounds are either cyclic or linear in structure. Because they are not chemically bound to the gel matrix, these chemicals are free to migrate if the implant ruptures. Moreover, the smaller sized molecules are known to permeate more easily through the implant shell.

The amount of linear and cyclic siloxanes released will depend on:

- the concentration of these low molar mass components;
- the rate of diffusion through the shell – which is amplified by swelling and diminished by the presence of barrier layers;
- whether the implant is ruptured;
- the cohesiveness of the gel (if the implant is ruptured). A cohesive gel will retain the shape of the original implant and retain within it much of the free silicone liquid, even when the shell is ruptured.

Some penetration of substances from the surrounding medium into the implant will also occur. One recent study (Beretta et. al. 2013) identified the presence of small amounts of cholesterol in the gel of one explanted PIP implant. In a clinical study, one-third of the not-ruptured implants were found to be yellow (see also table 3). This is explained by

the presumable uptake of substances from the serum (Chummun & McLean, 2013).

Similar results have been reported (Nakamura et. al., 1991) for silicone implanted in the eyes of rabbits. This indicates that besides leakage of silicone components across the shell there is also uptake of lipophilic molecules from the body into the implant. The relevance of these observations for the health risks of the silicone breast implants are yet unknown and needs further investigations.

The Australian TGA have examined explanted PIP implants and found among 107 explants variations in gel condition.

Table 3: Appearance of gels in ruptured and non-ruptured explants

Gel Condition	Ruptured	Not Ruptured	Total
Yellow	45	14	59
Clear	0	31	31
Opaque	5	12	17
Non-Uniform*	10	15	25
Oily*	27	17	42
Single Mass*	5	7	12

** A highly cohesive gel is desirable in case an implant ruptures. Highly cohesive gels are uniform, are in a single mass (as opposed to being in several pieces) and do not have a lot of free oil on the surface.*

Note: The descriptions used in this table are not mutually exclusive. In some cases more than one of the terms was used to describe the gel appearance. (ref. http://www.tga.gov.au/safety/alerts-device-breast-implants-pip-130211-testing.htm)

Clinical experience indicates that implants from other manufacturers can be clear, yellow, opaque or oily, but not non-uniform. (Hölmich and Eismann-Klein, personal communication). This gives additional evidence of the variability between PIP implants. The observations confirm the uptake of lipophilic molecules into the implant, but also demonstrate that the physical characteristics of PIP implant gels are variable, indicating poor control over the manufacturing process.

The TGA also conducted screening tests for over 60 volatile organic compounds of toxicological concern used in industry. The screening tests were carried out by two separate laboratories on samples from 10 different batches of PIP implants. No volatile organic compounds could be detected

The UK Expert Group also arranged for the testing of PIP implants. Five samples of PIP implants and 6 batches of other brands of approved breast implants were examined. The PIP implants were selected to represent a range of batch numbers and expiry dates. The analysis utilized FTIR (Fourier Transform Infrared Spectroscopy), GC-MS (Gas Chromatography Mass Spectrometry) and ICP-MS (Inductively Coupled Plasma Mass Spectrometry). The key findings were that there was no evidence of any significant organic or inorganic chemicals present other than siloxanes and there was no significant batch to batch variation in the test results. However, the tests did conclude that compared to the approved gels, PIP silicone gels contained significantly increased levels of low molecular weight cyclic silicones. (See table 4).

5.4. Cyclic silicones in PIP implants

So far, attention has focused on three low molar mass cyclic silicones namely D4 (octamethylcyclotetrasiloxane), D5 (decamethylpentasiloxane) and D6 (dodecamethylcyclohexasiloxane). These chemicals are often referred to collectively as cyclomethicone (SCCS, 2010).

As mentioned earlier, the UK MHRA commissioned Gas Chromatography/Mass Spectroscopy (GC/MS) tests on PIP and other implant materials. The tests showed that D4, D5 and D6 are present in higher concentrations in PIP implant gels compared to other breast implants. The TGA also conducted GC/MS tests on PIP implants and confirmed that D4, D5 and D6 are present in higher concentrations in PIP implants than in another brand of implants that was made by using the same Nusil™ MED3 6300 silicone raw materials as used by PIP when they initially obtained market approval. PIP implants exhibited detectable amounts of D4, D5 and D6 while these chemicals were below the limits of detection in the compared implants. Subsequently, the TGA used the presence of these compounds in the gel as a marker that the implant had been made using unapproved materials. D4 D5 and D6 were detected in all of the explants that were received by the TGA for examination, but the method of detection did not allow quantification.

Gel Permeation Chromatography conducted by the TGA determined that also other cyclic silicone materials were present in breast implant gels, not just D4, D5 and D6, in particular also higher order cyclic siloxane compounds and their linear analogues.

Beretta and Mallaco, (2013) tested gel samples from a PIP explants and a McGhan explant using GC/MS. They confirmed high levels of D4, D5 and D6 in the gels from both types of breast implant, but also found quantities of several other cyclic siloxanes and their linear analogues.

The Swedish Medical Products Agency (MPA) conducted extensive testing to quantify the levels of D4, D5 and D6 in PIP and non-PIP implants. They confirmed previous work that showed that all implants contained low levels of these cyclic siloxanes, but their concentration was particularly high in textured PIP implants. The same study showed that micro-textured PIP implants had relatively low levels of D4, D5 and D6.

Levels of D4-D6 in Nusil MED3 6300 gel (the product included in the CE approval for PIP implants) have been determined by the French Authorities as between 50 and 70 parts per million (ppm). Chemical analyses conducted by the Swedish MPA and the TGA report have found the following D4, D5 and D6 concentrations:

Table 4:Levels of D4, D5 and D6 in devises from various manufacturers

	D4 (ppm)	D5 (ppm)	D6 (ppm)
TGA – PIP*	136	434	474
TGA – Nusil	ND**	ND	ND
MPA – PIP2*	134	457	604
MPA – PIP Nusil*	ND	18	30
MPA – Brands A and B	ND	20	22
MPA – Brand C	30	72	132

* ***TGA tested several samples – the median result is quoted here. MPA tested one new implant and one explant of each PIP2 and PIP-Nusil; the highest result is quoted here.***

** ***ND = not detected***

5.5. Conclusions from Physico-Chemical Studies on PIP implants

The important conclusions that can be drawn from the studies on the properties and composition of PIP implants and how this compares with the properties and composition of the implants of other manufacturers are:

- Physical and mechanical tests suggest that the properties of PIP shells were comparable to those of other implants and met the requirements of international standards. However, researchers agree that variation in quality parameters, such as differences in shell thickness within and between samples, is high in PIP implants (TGA testing updates, ANSM 2013, Swarts et al 2013). This indicates inconsistencies in the manufacturing process that could explain higher rates of rupture.

- There is some indication that PIP implants underwent several "eras" of production in which unauthorised gel may have been used. For example the micro-textured PIP implants that were tested by the Swedish MPA contained relatively low levels of D4, D5 and D6, compared to (macro) textured PIP implants.

- The visual appearance related to cohesiveness and other qualitative parameters such as clarity and oiliness is highly variable in PIP implants, and again indicates inconsistent manufacturing.

There is unanimous agreement in the data evaluated that PIP implants contain higher levels of the cyclic siloxanes D4, D5 and D6 compared with PIP implants made with authorised gels, and implants of other manufacturers in general.

6. TOXICOLOGICAL PROPERTIES OF PIP IMPLANTS

6.1. Human exposure to siloxanes

No organic or inorganic contaminants have been found in PIP silicone. The attention is, therefore, paid to the low molecular weight siloxanes found in these implants. It must be emphasised that human exposure to these chemicals is not confined to PIP implants. In fact, low molecular weight siloxanes are present in a very wide range of consumer products. Examples include:

- cosmetics and other personal care products where the siloxanes are incorporated because of their antistatic/emollient/humectant/solvent/viscosity controlling/hair conditioning properties (SCCS 2010);
- food products, where they are used, for example, as antifoaming agents. Silicon in the diet has been claimed to be beneficial to health (EFSA 2011) It is noted that one siloxane, monomethylsilanetriol, has been proposed as a nutritional supplement (i.e.; a bioavailable form of silicone). However, evidence to date is insufficient to support this use (EFSA 2009);
- other domestic products such as cleaning and polishing agents, furniture, electronics and paints. Important properties utilized are low surface tension, high thermal stability and smooth texture;

A US estimate is that from use of cosmetic products alone women may be exposed to around 300 mg of total siloxanes per day (Horii and Kannan 2008). As a consequence these siloxanes can be detected in human body fluids and organs (Barnard et al., 1997, Lennart et al., 2005). Particular interest has centred on the three cyclic siloxanes D4, D5 and D6.

Of particular relevance is the fact that a study in Sweden of normal women who had never had breast implants, found that 11 out of 49 subjects had detectable levels of siloxanes in their breast milk (Lennart et al 2005).

6.2. Issues to be addressed

Are there new data on the key questions that need to be addressed namely:

- Do PIP implants represent an increased risk to human health compared to conventional medical grade implants?
- Is it possible that PIP silicone (either the polymeric material or the low molecular weight siloxanes) is associated with the increased incidence of local inflammatory reactions that have been reported with PIP implants compared with medical grade implants? (NB The use of data on implants from other manufacturers is very important in order to identify anything that appears unusual about PIP implants).

The following paragraphs summarize the conclusions reached. These are based to a large extent on the opinions reported by the Swedish Health Authority (Lakemedelsverket 2013.), and reports from various national bodies (including the UK MRHA, and the SCCS Opinion on D4 and D5; SCCS 2010). No new data has been identified on the toxicokinetics of the gel, nor on its adverse effects, consequently this analysis is focused on the properties of D4, D5 and D6.

6.3. Toxicokinetics

In the previous SCENIHR Opinion the available data on the general effects of the PIP implant contents were analysed. Here the focus is on siloxanes D4, D5 and D6 as they have been found at substantially higher levels in PIP implants compared to implants produced with medical grade silicone.

6.3.1. Uptake of D4, D5 and D6

D4, D5 and D6 are of low molecular weight and are volatile and lipophilic with low water solubility.

D4

Dermal. Pharmacokinetic modelling of dermal absorption in human volunteers indicated that 0.12% and 0.30% of applied D4 was absorbed into the systemic circulation for men and women, respectively. For risk assessment purposes a value of 0.5% for dermal absorption is appropriate (SCCS 2010).

Oral. D4 is most readily absorbed when delivered in corn oil. Other studies also indicate that the oral absorption of D4 can be significantly influenced by its carrier substance.

D5

Dermal. Pharmacokinetic modelling of dermal absorption in human volunteers indicated for men and women that 0.05% of applied D5 was absorbed into systemic circulation (SCCS 2010).

Thus, on average less than 1.0% of applied D4 and D5 combined appear to be absorbed in vivo, with the majority remaining in the skin.

D6

D6 is anticipated to have rather similar toxicokinetic properties to D5.

D4 and D5

From Implants

In order to consider the fate of released cyclic siloxanes from implants it is necessary to identify the nature of the tissue capsule surrounding the implants. The tissue capsule arises due to a chronic proliferative inflammation pattern induced by the implant starting with synovial like metaplasia of proliferating mesenchymal cells and ending with transformation into a dense fibrosis (Siggelkow et al 2003). A mature capsule comprises: at the implant surface massive deposits of fibronectin beneath which is a single layer or multilayer of fibroblasts, macrophages and Langerhans-like dendritic cells, together with heat shock proteins. The capsule tends to be well vascularised. Below this is a layer(s) of dense connective tissue (actin plus smooth muscle cells) (Wolfgang et al., 2004).

Tissue capsules can vary substantially with regard to thickness and developing calcification (Siggelkow et al 2003).

When an implant leaks or ruptures unbound siloxanes including D4, D5 and D6, will be released, at least partially, into the space between the implant and the fibrous capsule, which may contain fluids (periprosthetic fluid). The fibrous capsule, providing it remains intact, may then act as a barrier to further dispersal of siloxanes within the body. It is not clear yet to which degree this is a barrier to the further migration of D4, D5, D6 or other siloxanes.

It has to be assumed that ruptured PIP implants will result in exposure to the siloxanes D4, D5 and D6 although the release into the body outside the capsule compartment may be slow.

6.3.2. Metabolism

The primary metabolic fate of D4, D5 and D6 is oxidation. This appears to be mainly mediated by various cytochrome P450 enzyme isoforms. Dimethylsilanediol and methylsilanetriol appear to be the major metabolites of D4. Comparable metabolic pathways occur for D5 and D6. These metabolites are formed both in rats and man. It is also likely that they will be produced in *in vitro* test systems such as the Ames test with added S9. In addition, there is evidence from one report that oxidation/hydrolysis of D4 may occur in the lymph nodes mediated by macrophages (Pfleiderer et al. 1999). Significant metabolism/abiotic conversion of the siloxanes is probably unlikely in the periprosthetic fluid. Thus, estimates of penetration of the capsule may be confined to the parent siloxanes.

6.3.3. Distribution

D4, D5 and D6 tend to be more concentrated in fat and skin than in other tissues. This is attributable to their high lipophilicity. In fat, levels of siloxanes may be up to 100 times greater than in the blood. However, from chronic studies in animals there is no evidence for increasing bioaccumulation of D4 and D5 over time (SCCS 2010).

Studies in a small number of women with breast implants have found levels of D4 in blood of 79-92 ng/ml, and for D5 of 28 ng/ml (one subject only). In adipose tissue the levels were up to 1.4 µg/g for D4 and up to 0.74 µg/g for D5 (Flassbeck et al., 2003).

As noted above, all women, regardless of whether or not they have breast implants, are likely to have measurable levels of D4, D5 and D6 in their tissues. Studies in women with breast implants by Flassbeck et al. (2001) showed that there were detectable levels of the silicones in various tissues, even several years after the removal of their implant. However, no measurements were made of a relevant control group.

In another study reported by Flassbeck et al (2003) tissues samples were analysed for siloxanes from women who had had silicone breast implants explanted. Siloxanes (D4, D5 and D6) were found at levels of between 0.1 and 1.4 µg per gram of tissue.

However, it should be noted that even in women without breast implants siloxanes can be detected in various organs (Barnard et al., 1997, Lennart et al., 2005) due to exposure of siloxanes in cosmetic and household products and from other sources (Horii and Kannan 2008).

Various models have been developed to estimate the distribution of D4, D5 and D6 that might occur from a breast implant. In the model of Reddy et al (2007), it was estimated that in a worst case scenario 5.8% of these chemicals might be available for distribution to the tissues. However, this value would need to be substantiated, as it has not been experimentally verified.

Most of the D4, D5 and, D6 which do pass the capsule are likely to either be cleared via the blood and lymph or, because of the lipophilic nature of siloxanes, to be deposited in local fatty tissue. D4 is readily exhaled intact due to its low blood: air partition coefficient resulting in Exhalation of approximately 80% (SCCS 2010). For D5 when entering the circulation, the combination of properties - high metabolic clearance and low blood: air partitioning- serve to prevent significant bioaccumulation of this compound despite its tendency to be stored in lipids within the body following all routes of exposure (SCCS 2010).

6.3.4. Clearance

In rodent studies, elimination is fairly rapid from the blood, but much slower from fatty tissues. Exhalation appeared to be a relevant and major route of clearance of D4 and D5, a consequence of a low blood/air partition coefficient. Polar metabolites have enhanced water solubility and are thus mainly excreted via the urine (SCCS 2010).

With regard to the health of the nursing child, the levels of siloxanes in breast milk need to be considered. A Swedish study from 2005, conducted by the Swedish Environmental Research Institute, as part of a national screening programme, measured the levels of siloxanes D4, D5 and D6 in human breast milk of 49 women without any form of breast implant (Lennart et al., 2005). The maximum levels found in 11 of the 49 women were as follows: D4, 10 µg/l; D5, 4.5 µg/l; D6, 4.8 µg/l. The highest level of total siloxanes recorded was between 13 and 14 µg/l (13-14 ppb).

In 1998 (Semple et al., 1998) and in a review from 2007, (Semple 2007) women with breast implants (but not PIP implants) were compared with women without implants. It was found that mean silicone levels did not differ in either breast milk (55±35 and 51±31 ng/ml, respectively) or in blood (79±87 and 104±112 ng/ml, respectively). There was no information about the rupture status of the silicone breast implants. These data provide further evidence that women without breast implants have levels of siloxanes in their bodies that are similar to those in subjects with breast implants. In the same study it was noted that the mean silicone level measured in store-bought cows' milk was 709 ng/ml. The silicone levels in alternative sources of infant nutrition were much higher. In 26 brands of commercially available infant formula siloxane levels were as high as 4402 ng/ml (Semple et al., 1998). Also in studies commissioned by the UK MHRA significant levels of siloxanes were found in a sample of cows' milk (MRHA 2012c).

Regarding silicone in the breast milk of a woman with ruptured PIP implants, only one case has been reported (MHRA 2012c): A single sample of breast milk was obtained from a lactating donor with ruptured PIP implants. The sample was analysed for the presence of total silicones, including low molecular siloxanes. Although the method of testing was not validated, and may thus lack precision, the level of total silicones was less than 100 ng/ml (equivalent to less than 100 parts per billion [ppb]). This value is not greatly different from that of cows' milk and lower than the findings for various infant nutrition supplements. However, no reliable conclusions can be derived from a single case In particular, important data are missing such as the amount of leaked silicone and the duration of persisted leakage.

With regard to toxicokinetics it may be concluded that D4, D5 and D6 do not readily pass biological membranes. Siloxanes that are absorbed tend to concentrate in fatty tissues. The metabolic fate involves oxidation to more polar and water soluble metabolites. Although not specifically studied, there is no reason to assume that other siloxanes would have different toxicokinetic properties to those of D4, D5 or D6.

6.4. Toxicological properties of siloxanes

6.4.1. Cytotoxicity, irritancy and inflammation

Testing by AFSSAPS (Agence française de sécurité sanitaire des produits de santé) in 2010 showed the absence of cellular cytotoxicity by PIP silicone. More recently cytotoxicity tests commissioned by TGA (Australian Therapeutic Goods Administration) have yielded the same negative result. Additional cytotoxicity tests commissioned by the MHRA (Medicine and health care products regulatory agency UK) were also uniformly negative.

In 2010 AFSSAPS reported that PIP silicone was positive (displayed skin irritant potential) in a rabbit assay in which the test material was administered intradermally.

More recently the TGA commissioned two separate studies, one performed in Australia and a second in Europe. In both instances all batches of test material, including organic and aqueous extracts of PIP silicone and PIP implant shells, were uniformly negative for irritant activity. The conclusion, based on all the data available, was that silicone from PIP implants lacked the potential to cause skin irritation. Since then the MHRA commissioned an additional and separate *in vitro* assay for skin irritation and that also was negative.

When tested individually D4, D5 and D6 appear to be non-irritants in standard tests.

However, in one study (Pfleiderer et al 1999) 1 ml of an aqueous emulsion of a mixture of cyclic siloxanes that is described as predominantly D4, at a concentration of 9.6%, was injected into the thigh muscle of rats either as a single or repeated administration. Expressed as ppm or in terms of mg/kg body weight the level injected is two orders of magnitudes higher than that, which could arise from a ruptured breast implant. In that study, local cytotoxicity was observed and presence of siloxanes detected in the draining lymph node. The clinical relevance of this to the possible situation in which D4 might be released from a PIP implant needs to be evaluated very carefully bearing in mind the following factors:

- the doses are very different;
- injection of a high volume of fluid into a muscle can by itself cause adverse effects;
- in contrast to the experimental conditions in the Pfleiderer et al. study (1999), following an implant rupture the siloxanes tend to remain in the gel. Therefore, the tissues are not expected suddenly to be exposed to a high dose;
- the rat model used has not been validated. Injection of one ml of a relatively unstable aqueous emulsion into the thigh muscle could provoke an adverse effect, regardless of its lipophilic component;
- the nature and levels of contaminants in the preparation used were not determined;
- based on a lack of clinical signs and lack of local toxicity (skin lesions scored according to Draize), a no observed adverse effect level (NOAEL) of 960 mg/kg bw was found in a repeated dose study in rabbits with dermal application of D4 for 28 days.

It can be concluded that D4, D5 and D6 are, at most, very weak irritants.

6.4.2. Genotoxicity

Studies commissioned by the MHRA and AFSSAPS in 2010, along with those conducted by Dow and other companies (cited in SCCS 2010), have shown that PIP silicone lacks genotoxic potential. Additional genotoxicity tests commissioned by the MHRA in 2012 were also negative.

6.4.3. Conclusions on the effects of an acute release

Collectively these data provide persuasive evidence that silicone derived from PIP implants, and siloxanes D4, D5 and D6 are not genotoxic and lack the potential to cause either cellular cytotoxicity or skin irritation.

The data summarised above failed to disclose any acute toxic properties of silicones derived from PIP implants or of siloxanes D4, D5 and D6.

Moreover, these data show that siloxanes display only very low acute toxicity following exposure by the oral, dermal or inhalation administration. They also fail to cause eye irritation or skin sensitisation.

6.4.4. Chronic toxicity and carcinogenicity studies

It is nevertheless appropriate to consider also the chronic toxicity of siloxanes and whether their increased concentrations in PIP implant silicone represents a health risk.

In this context it is important to acknowledge again that siloxanes are used in a wide variety of applications, including: sealants, paints, cosmetics and personal care products, waxes and polishes, textiles, paper coatings, mechanical fluids and others. Such exposures collectively may lead to detectable levels of siloxanes in the body. Thus, in 2005 results from the Swedish National Screening Programme were published by the Swedish Environmental Research Institute, and as part of that survey which focused on siloxanes, breast milk samples from 49 unselected and unidentified women were analysed. Eleven of those 49 samples were found to contain detectable levels of one or more of D4, D5 and D6 (Lennart et al., 2005).

D4

D4 has been assessed in a range of toxicity studies by different routes of exposure. Repeated dose studies, at relatively high oral and inhalation doses, identified few systemic effects. Clinical signs of toxicity were minimal. Reversible liver enlargement (hypertrophy) and phenobarbitone-like increases in xenobiotic metabolising enzyme activities were found. These effects are considered to be an adaptive response to xenobiotics, reversible upon cessation of exposure and not associated with overt hepatotoxicity.

D5

Endometrial adenomatous polyps and adenocarcinomas were observed in rats exposed by inhalation to D5 for two years, but were not observed after one year of exposure, or after a further one year exposure free period (Dow 2005). The carcinogenicity of D5 in rats after inhalation exposure was significant only at the highest concentration of 160 ppm (192 mg/kg bw). There is doubt that the uterine tumours observed are relevant to humans. in any event carcinogenicity was observed in rats only at much higher exposure levels than could occur following a rupture of a PIP implant.

6.4.5. Reproductive toxicity

It has been reported (Scientific Committee on Consumer Products, 2005) that inhalation exposure of rats to D4 was associated with delayed ovulation and reduced fertility. The 'No Observable Adverse Effect Level' (NOAEL) was judged to be 300ppm by inhalation. On that basis siloxane D4 is regarded for regulatory purposes under the CLP (Classification, Labelling and Packaging) regulations as having adverse effects on fertility.

Although D4 shows very weak estrogenic activity in a rat uterotrophic assay (McKim et al., 2001), the reproductive toxicity observed is believed not to be attributable to a direct oestrogen receptor (ER)-mediated effect. Rather it is proposed that the effects seen are due to D4 causing a delay or blockage of the luteinising hormone surge that is required for optimal timing of ovulation.

"It can be concluded that the reproductive effects of D4 in female rats and mice are related to rodent specific imbalance in the normal hormone milieu. Such imbalances are common in rodents and are of little relevance to humans" (SCCP 2005).

6.4.6. Immunological effects

Siloxanes do not cause skin sensitization. Studies in rats have found that D4 does not cause immunotoxicity (Looney et al., 1998; Burns-Nass et al, 2003; Klykken et al, 1999).

Human volunteers have been exposed orally, or by inhalation, to D4 with no pro inflammatory or immunotoxic effects having been found (SCCS, 2010).

It can be concluded that D4 and D5 are not sensitisers and do not have immunotoxic properties.

6.5. Overall conclusions

No new data are available of the toxicokinetics or the effects of the polymerized gel. In respect of the low molecular weight siloxanes:

- Data made available since the 2012 SCENIHR opinion on PIP implants, no longer support the conclusion included in this opinion regarding the irritant nature of the contents of PIP devices. That conclusion had been based on a single test result, which could not be reproduced in subsequent investigations. It can now be concluded that the silicone used in PIP implants is not irritant.
- From the evidence available, it appears very unlikely that D4 and D5 cause the inflammation that is reported in some patients after implant rupture.
- Studies in laboratory on animals show that D4 and D5 are unlikely to pose a health risks with regard to either patient health and/or the health of the foetus or nursing infant.
- Individuals, regardless of whether or not they have a breast implant, and whether or not it is intact, have measurable blood levels of D4, D5 and D6 in their tissues. This is due to exposure of siloxanes used in a wide variety of applications. Ruptured PIP implants are likely to result in increased blood and/or tissue levels of D4 or D5, but these will nevertheless remain well below the levels that might be associated with adverse health effects.

Although a number of other siloxanes present in PIP implants have not been studied specifically, it is assumed that their toxicity would not differ significantly from that of the well-studied cyclic siloxanes D4 and D5. It is noted that long chain siloxanes are not associated with toxicological effects (Nair and Elmore 2003) It seems very unlikely, therefore, that the higher levels of low molecular weight siloxanes, released as a consequence of a PIP implant rupture (compared with that of other breast implants), would result in an increased risk of adverse health effects.

There is no convincing evidence that the risk for adverse effects after rupture of PIP-implants is higher than the risk after rupture of silicone breast implants from other manufacturers. The overall risk is higher for PIP-implants due to the higher risk of rupture.

7. CLINICAL FINDINGS

7.1. Results from the SCENIHR questionnaire

A questionnaire was developed in the scope of the mandate received for this opinion. It has being hosted on the website of the European Union since November 2012, and can be accessed on http://ec.europa.eu/yourvoice/ipm/forms/dispatch?form=PIP2final&lang=en.

The outline of the questionnaire can be seen in Appendix 1. The aim of the study was to prospectively collect information about all kinds of explantations; for PIP implants as well as other implants, so that comparisons and benchmarking could be made. Unfortunately, not many responses were obtained. The overall majority of the responses were about PIP implants. By 23rd April 2013, information about explantation of 253 implants had been received; of these 229 were PIP implants and 6 Rofil implants.

Eighteen percent of PIP and Rofil implants were ruptured. The results of the survey obviously did not represent a continuous prospective reporting of European explanations, but rather an arbitrary sub-cohort. The total number of responses was too low to make firm conclusions on the outcomes. However the PIP rupture rates appear to be in compliance with those of the larger UK and French findings (see below).

7.2. Reports of government committees and agencies

Since the SCENIHR report was made public in February 2012, reports from the French health authorities, a UK and an Australian expert group, respectively, have been published. Very recently, the Swedish Medical Product Agency published their evaluation. Preliminary data from Spain were also available and were included. The main findings from these reports are summarized below. It should be noted that in the past there were less investigations on the adverse effects of breast implants. In addition there is far less data on implants from other manufacturers than there is for PIP implants.

7.2.1. UK data

The National Expert Group (MHRA 2012) requested that the Medicines and Healthcare Products Regulatory Agency to contact all major hospitals and clinics performing breast implant surgery to ask them to complete a questionnaire seeking information for both PIP and other brands on:

- the total number of women per annum who received implants between 2001-2011;
- the reasons for explantation, and the clinical findings at explantation, of all explantations carried out over the same period;
- the reasons for explantation and the detailed clinical findings at explantation for all PIP implants removed from February to May 2012.

Based on the responses it was found that approximately 131 000 women received some 238 000 implants during the period of 2001-2011, of whom 28 000 women received PIP implants. Data are not based on individual medical files, but rather on estimates from the major hospitals and clinics.

More detailed findings from 5870 branded explants were reported, of which 5575 had an implant date (MHRA, 2012b). Raw rates were computed, as a percentage of all women with each brand of implant, for:

- all explants;
- explants in which an implant failure was found ('finding at explant', any of 'rupture already known', 'rupture unexpected finding', ' significant silicone bleed' in either implant OR reason at explant 'signs of inflammation, silicone leak without evidence of rupture');
- explants in which clinical signs were found (any of 'breast inflammation or lumpiness', 'lymphadenopathy' in either implant OR reason at explant 'signs of inflammation, silicone leak without evidence of rupture').

Approximate survival analysis was carried out for all three types of outcome, using (year-of-explant - year-of-implant) as the survival time, and (2012 -year-of-implant) as the follow-up for cases that had not been explanted.

The UK expert group (MHRA 2012 a, b) reached the following conclusions on the basis of the retrieved data:

Overall explant rate. There is little evidence of PIP having an overall explant rate greater than other implants prior to the concerns regarding PIP devices being recognized.

Rate of explant of PIP implants with an implant failure: Survival estimates (or more correctly: estimates of failure) for all PIP implants were: 1.2% at 5 years; 3.1% at 10-years; this is around 4.5 x rate of other branded implants (RR ~ 4.5). Considering only pre-January 2010 explants (before the media attention), the estimates were lower but retain the excess risk from PIP: 0.6% at 5 years, 0.9% at 10 years, (RR ~ 2.8). For non-NHS augmentation implants the relative risk was higher, around 5. Few PIP implants were used for NHS reconstruction, but an excess risk was still observed. *Overall, a relative risk of around 2-6 is reasonable*.

Rate of explant with clinical signs: Survival estimates (read: failure estimates) were; 0.7% at 5 years; 1.9% at 10-years; this is around 3-4 x rate of other branded implants (RR ~ 3-4). Considering only pre-January 2010 explants, the estimates were lower but retain the excess risk from PIP: 0.4% at 5 years, 0.6% at 10 years, (RR ~ 2.0). Other subgroups showed a pattern similar to implant problems. *A relative risk of around 2-5 appears appropriate.*

The UK expert group (MHRA 2012, a, b) highlighted some important limitations:

- implant numbers are necessarily approximate;
- some explants may be from other centers and hence not directly relate to the implant totals for each center;
- degree of follow-up is unknown, and would be expected to be low for private clinics. Hence explants will generally be undercounts;
- since March 2010, publicity surrounding PIP implants has led to additional concern and explants, particularly since December 2011, and this could bias the results against PIP. Calculations have been performed for pre 2010 explantations;
- PIP implants have generally been used for augmentation in private clinics with limited follow-up, and rarely in NHS hospitals for reconstruction, which tend to have better follow-up. This will, if anything, bias the results in favour of PIP.

Therefore it is not possible to make precise estimates on the basis of the available data, and a considerable degree of judgment is required to interpret the results. Ninety five percent confidence intervals are provided for the relative risks (PIP/non-PIP ratios) but the large sample sizes will give an undue precision to the results, whereas the uncertainties arise more from limitations in the follow-up.

Analysis of the findings at 5870 explant operations (including 1565 PIP explants) identified the following (NB. All comparisons reported below are statistically significant at the 0.1% level):

- 31.1% of PIP implants had device failure compared to 4.3% among non-PIP implants (RR = relative risk ~ 7.3), defined as any of 'rupture already known',

'rupture unexpected finding', or 'significant silicone bleed' in either implant;

- 16.9% of patients with PIP explants had clinical signs compared to 3.7% of patients with non-PIP implants (RR = ~ 4.6), defined as any of 'breast inflammation or lumpiness', 'lymphadenopathy';
- there was no excess of capsular contracture, haematoma, infection or post-implantation breast cancer cases among women with PIP implants compared with women with other implants.

Restricting to explants before January 2010 made no important differences to the findings.

The UK expert group (MHRA 2012 a, b) examined the prevalence of clinical problems, splitting explants into those done for a perceived problem and those performed for other reasons.

The below Table 5 shows that, if the explant was performed due to an implant problem, there was no difference between PIP and non-PIP implants as to the prevalence of clinical signs. In those explants carried out without a perceived implant problem, the prevalence of clinical signs was slightly higher in PIP implants, but only 6% compared to 2%.

Overall, of 264 women with PIP implants with clinical signs found at explantation, 209 (79%) were identified before the explantation.

Table 5: Prevalence of clinical signs ('inflammation' and/or lymphadenopathy) at explant for PIP and non-PIP implants, depending on whether or not explantation was performed due to a perceived problem

	Explant due to problem			**Explant not due to problem**			**All explants**		
	n	Clinical signs	%	n	Clinical signs	%	n	Clinical signs	%
Not PIP	219	67	30.6%	4200	92	2.2%	4419	159	3.6%
PIP	569	209	36.7%	999	55	5.5%	1534	264	17.2%
PIP/non-PIP ratio			1.2			2.5			4.8
95% intervals			1.0 to 1.5			1.8 to 3.5			4.0 to 5.8

A prospective study was undertaken after January 2012, asking surgeons to report findings during explant surgery of PIP implants. 761 women were operated on and their data are included.

Reasons for explanation were requested, and if the explant was for a perceived problem, 64% had device failure, compared to 23% when the explant was for anxiety alone. The rates for clinical signs were substantially higher for explants due to perceived problems: for explants due to anxiety alone, only 2% had clinical signs; For those with a failed implant who had been explanted due to anxiety alone, 11/118 (9%) had clinical signs compared to 90/165 (55%) in those who had a failed implant and had been explanted due to a perceived problem; Of the 101 with clinical signs, 90 (89%) had been detected as having a problem prior to explantation. In summary it is concluded that although silent ruptures are common, such ruptures were infrequently associated with severe clinical problems.

Table 6: Findings in 761 explants of PIP devices since January 2012.

	Finding in at least one of the implants removed	**'anxiety alone' n=504**	**'not just anxiety' n=257**	**Overall n=761**	**% in 'Anxiety alone'**	**% in 'not just anxiety'**	**% in overall**	**P**
1	Some degree of implant failure (rupture or severe bleed)	118	165	283	23%	64%	37%	<0.001
2	Silicone granuloma ta	2	16	18	0.4%	6%	2%	<0.001
3	Axillary lymphadenopath	1	31	32	0.1%	12%	4%	<0.001
4	Loss of cohesion	37	107	144	7%	42%	19%	<0.001
5	Inflamed	33	83	116	7%	32%	15%	<0.001
6	Capsular contractur	46	37	83	9%	14%	11%	0.02
7a	Silicone granuloma	5	18	23	1%	7%	3%	<0.001
7b	Silicone granuloma	0	6	6	0%	2%	1%	0.01
7c	Silicone granulomat a multiple	0	6	6	0%	2%	1%	0.001
8a	Silicone related lymphadenopath y –small solitary	2	22	24	0.4%	9%	3%	<0.001
8b	-small multiple	1	22	23	0.2%	9%	3%	<0.001
8c	-large solitary	1	11	12	0.2%	4%	2%	<0.001
8d	-large multiple	0	16	16	0%	6%	2%	<0.001
8e	-matted	0	2	2	0%	0.8%	0.3%	0.11
9	Lymphadenopat hy elsewhere	0	2	2	0%	0.8%	0.3%	0.11
10	Clinical signs with intact implant (2 or 3)	4	39	43	1%	15%	6%	<0.001
11	Clinical signs with ruptured implant (7, 8 or 9)	11	81	92	2%	32%	12%	<0.001
12	Any clinical signs (2, 3, 7, 8, 9)	11	90	101	2%	35%	13%	<0.001

Based on the UK data, the most important clinical conclusions regarding the PIP implants are:

- PIP implants are significantly more likely to rupture or leak silicone than other implants, by a factor of around 2-6, and this difference is detectable within five years of implantation;
- The failure rate for PIP implants is estimated on the basis of these reported adverse events at 1.2% at five years, rising to 3.1% at 10 years. This compares with a failure rate for other brands of silicone gel implant of 0.2 - 0.4% at 5 years and 0.5 - 1.1% at 10 years. However, the true underlying failure rate, including 'silent' ruptures, will be greater than this;
- PIP implants are 3-5 times more likely than other implants to result in local clinical signs;
- The rate of explants with local clinical signs is 0.8% at five years rising to 2.1% at 10 years. 'Silent' ruptures (ruptures which come to light only on explantation) are not generally associated with these local reactions;
- PIP implants are not associated with higher risks of other clinical problems such as capsular contracture, haematoma or cancer than other breast implants.

Comment on the UK data

It is an impressive data collection and the largest to date[2], both on nationwide implantation in general and on PIP implants in specific. This is also the only report that includes bench-mark data from other implant brands for comparison. The data were obtained through contact with all major clinics and hospitals, which were asked to fill out pre-formed questionnaires about the number of women receiving implants of different brands during the period 2001-2011. It is not explained in the UK report exactly how the retrospective data was generated simply that data are estimates. Implant data can possibly most easily be obtained by revision of buying lists from different suppliers. This gives a rough but reasonable estimate, which suffices for the larger picture. It is not stated how large a percentage of those invited did indeed participate in providing data.

Regarding the explantation data, the surgeons were asked about possible reasons for explantation which could include suspected rupture, signs of local reaction without apparent rupture, problems with the contralateral implant, aesthetic appearance, or other reasons. These variables are quite specific and it is not possible to answer properly without evaluation of individual medical records of patients. It may be questioned whether clinics and hospitals routinely have a database to search from. Some may, but others probably not. It therefore should be asked how valid is this information? It could be the case, that retrieval of detailed information was a matter of the involved surgeons remembering the specific case, but perhaps not the case next to it. A recall bias "in favor" of PIP implants (with PIP being overrepresented) is possible. The UK expert group also discusses this. The validity of the data is without doubt an important potential confounder however difficult to judge for those not directly involved in data gathering.

Among the strengths of the UK data are that the information about PIP implants was benchmarked against breast implants from other manufacturers on the market at the same calendar time. With the PIP attention it is likely that adverse events among PIP implant patients could be over-reported compared to other implant brands. A subset analysis based on data before 2010 did not seem to change the picture, however, since it is retrospective data, a report bias could still be significant.

For the prospective data this could also be the case; probably not during reporting, more likely during observation/examination: knowing a patient had PIP implants could render the examining surgeon more attentive to signs of local inflammation for example, and thus more able to find it in the PIP implant receivers. Yet, underreporting is probably an even larger risk, both because this is generally the case unless prospective rigid registration is applied and because patients will be lost for follow-up.

[2] To the date of the preliminary opinion (September 2013)

7.2.2. French data

The Agence Française de Sécurité Sanitaire des Produits de Santé (AFFSAPS) and the later Agence Nationale de Sécurité du Medicament et des Produits de Santé (ANSM) has published reports about French women with PIP implants. The April 2013 report and the May 2013 update (unpublished data) is an extended update of their former publications based on reports of adverse reactions to the Agency.

It is estimated that 30 000 French women have PIP implants. By May 2013, 16 426 women with 28 276 PIP implants have had their implants removed and their data have been submitted to the ANSM. A certain underreporting and probably also delay in reporting is expected.

4 332 women have been operated because of clinical signs and/or findings.

12 094 women have been explanted prophylactically, i.e. because of the French government recommendations to explant all PIP implants. It is stated that in 20% of these women a malfunction of the implant was discovered; in 42% the implant was ruptured. In another 42% there was gel-bleed. Other malfunction accounted for the remaining 16%.

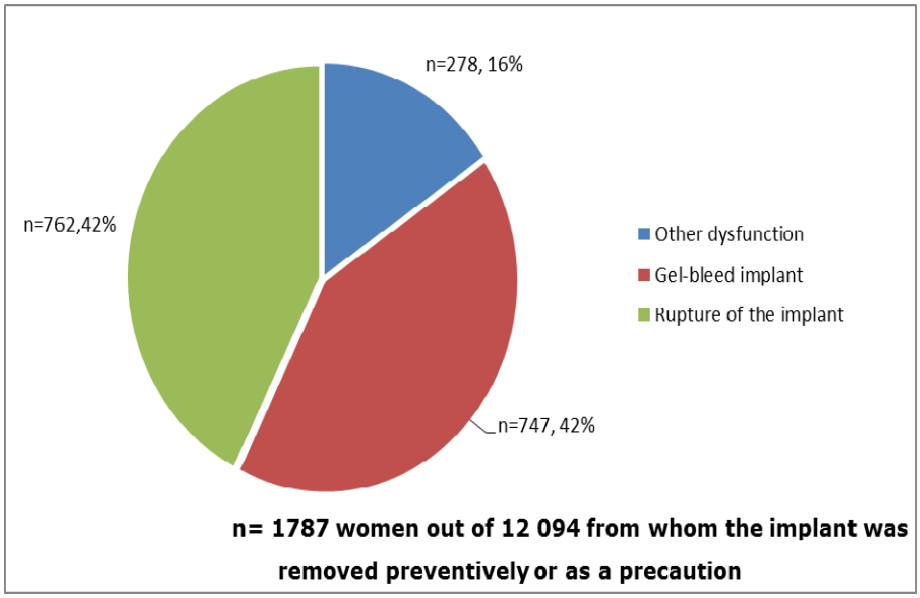

Figure 1. Number of women with malfunctioning implants encountered in preventive explantation.

Overall, 7 186 implants of the removed 28 276 implants (25.4%) in 5 434 women were found to be malfunctioning. Some of the implants had more than one malfunction; in total 7 618 malfunctions were registered. The most common defect was implant rupture, which was seen in 15.5% of all the implants in the study, followed by gel-bleed (7 % of all the implants). In 1.6% of all implants a change of the implant colour was observed. In 0.9% of all implants, folds or rotation was found, and in 0.4% of all implants other malfunctions were noted. Rupture and gel-bleed represented 84% of the malfunctions among PIP implants.

The majority of ruptures were found among implants of 5-6 years old. The median implant age at rupture was 5.9 years, and median time after implantation to treatment for symptoms or signs was 5.9 years.

In total, 4 670 undesirable effects were found among 2 883 women (17.6 % of all study women). Overall, per breast, 4 670 reactions in 28 276 explants (16.5%) showed a local reaction. The reactions are listed below:

Table 7: Categories of effect. Percentages are calculated from all 16.426 study women and 28.276 explants

Nature of the undesirable effect	N = 4,670 in 2882 women		
	Number	%/breast	%/ woman
Capsular contracture grade 3 and 4	2,153	(7.6 %)	(13.1 %)
Siliconoma, lymphadenopathy	1,248	(4.4%)	(7.6 %)
Seroma/effusion	532	(1.9 %)	(3.2 %)
Inflammation or infection	383	(1.4 %)	(2.3 %)
Other	354	(1.3 %)	(2.2 %)

A number of women (~2000) had ruptured implants but no apparent adverse effects.

A total of 70 cases of breast cancer in women with PIP implants were reported, and one patient died from ALCL (Anaplastic Large Cell Lymphoma). No additional cases of ALCL have been reported. This number is not considered exceptional since a certain number of breast cancers are to be found among such a large female population. The French National Cancer Institute has been consulted and has agreed on the above interpretation: *there are no data, to date[1], to evidence any additional risk of ALCL or breast adenocarcinoma specifically linked to PIP Protheses, compared with other implants.*

The ANSM confirm their recommendation of prophylactic removal of PIP implants.

Comments on the French data:

The French data represents the largest sample of actual incident reporting. Before March 2010, the reporting of data was from surgeons aware of increased problems with PIP implants. After the official decision to prohibit marketing, sale and use of PIP implants on 30 March 2010, reporting of adverse findings in PIP recipients increased, and since December 2011 when the French Ministry of Health approved and recommended explantation of all PIP implants, data from explanations have been numerous. By May 2013, close to 16.500 women have undergone an operation and have had their PIP implants removed.

The retrieval of explant data is impressive. The categorization of malfunctions in the French analysis is different from for instance the UK categorization, which makes comparisons somewhat difficult. Patients are stratified according to:

A: "signe d'appel" meaning if there were clinical signs and/or if sonography or other imaging examination found signs for implant rupture

B: no signs or findings, women were operated because of the health authorities recommendation to explant all PIP implants.

It is not clear from the data, how many of those with a sonography-diagnosed rupture did or did not have clinical signs. Inclusion of folds and rotations as a malfunction of the

[1] To the date of the preliminary opinion (September 2013).

implant could be argued to probably more often be due to pocket creation, thus a surgical problem or perhaps a problem due to capsular contracture, but not in itself a problem with the implant. In line with this, capsular contracture is a well described complication for all implant surgery and also found with other implant brands, but could also be more pronounced in case of local irritancy. In the UK findings, PIP implants did not account for more capsular contractures than the other examined implants. Capsular contracture can be a response to local inflammation, but many different causes have been suggested, of which subclinical infection with biofilm formation is probably the single most important cause (see below, section 7.2 Other conditions, Update on capsular contracture). To include this in adverse effects due to substandard PIP implants may not be justified and may cloud the picture.

Among 20% of prophylactically explanted women, implant malfunction and/or clinical signs of inflammation were found. Implant ruptures and other malfunctions and adverse effects were found in all age-groups of the implants, however median implantation time was 6.4 years and 6 years, respectively.

It can be concluded that the overall rate of adverse events with PIP implants, found to date in the French material was 16.5% (4 670 in 28 276 explants). If capsular contracture (n=2 153) is subtracted, this figure will be 8.9 % per breast (2 517/28 276) or 15.3% per woman (2.517/16.426). Any malfunction of the implant (including rupture) was found in 25.4% (7 186/28 276) of the implants; 15.6 % were ruptured (4.406 of 28,276) at time of surgery. These results are 5-8 times higher than the UK figures. As reported in the 2012 SCENIHR opinion on PIP implants (page 35), local complications among silicone breast implant recipients generally range between 17%-36%, and for instance in the FDA core study on Allergan implants, 15% of the study women had capsular contracture after 6 years of implantation (Spear 2007). In a parallel study on Mentor implants, 8.1% of women had significant capsular contracture after 3 years of implantation (Cunningham 2007). The probability of capsular contracture generally increases with increasing implantation time (Hölmich, 2007).

Numbers for lymphadenopathies and siliconomas (7.6%) are difficult to compare to similar populations with relatively short-term implantation, since this has not been reported consistently. In a study of long-term results, 21% and 6% of women had bilateral and unilateral axillary lymphadenopathy, respectively, 2% had silicone granuloma after a mean of 19 years of implantation. (Hölmich, 2007) In another study also primarily involving first and second generation implants, regional lymphadenopathy was found with 25% of implants, equally distributed among ruptured and intact implants. Median implantation time in that study was 16 years (range, 6-27 years) (Hölmich, 2005).

A court trial against the owner and director of the PIP factory is ongoing and as a consequence certain detailed information about the PIP implants and production methods is part of this trial and therefore not available in the development of this opinion.

7.2.3. Australian Data

Approximately 13 000 PIP silicone breast implants were supplied in Australia between 1998 and 2010, and it is estimated that about 5 000 women have been operated with PIP implants.

The Australian Department on Health and Ageing, Therapeutic Goods Administration (TGA) has collected information about the PIP situation in Australia. All information available is posted on the TGA-website http://www.tga.gov.au/safety/alerts-device-breast-implants-pip-130211.htm#information-consumers

Table 8: Rupture incidence

Reporter	Confirmed ruptures	Unconfirmed ruptures
Surgeons	320	10
Patients	107	12
Supplier	24	
All reporters	451	22

The TGA categorizes ruptures as 'confirmed' if there is sufficient information to uniquely identify the patient, the implant and x-ray or other diagnostic image showed rupture, or rupture was found during surgery. The information on ruptured implants suggests that the average time to rupture is between 5 and 6 years, although a small percentage of implants had been implanted up to 10 years before they were found ruptured.

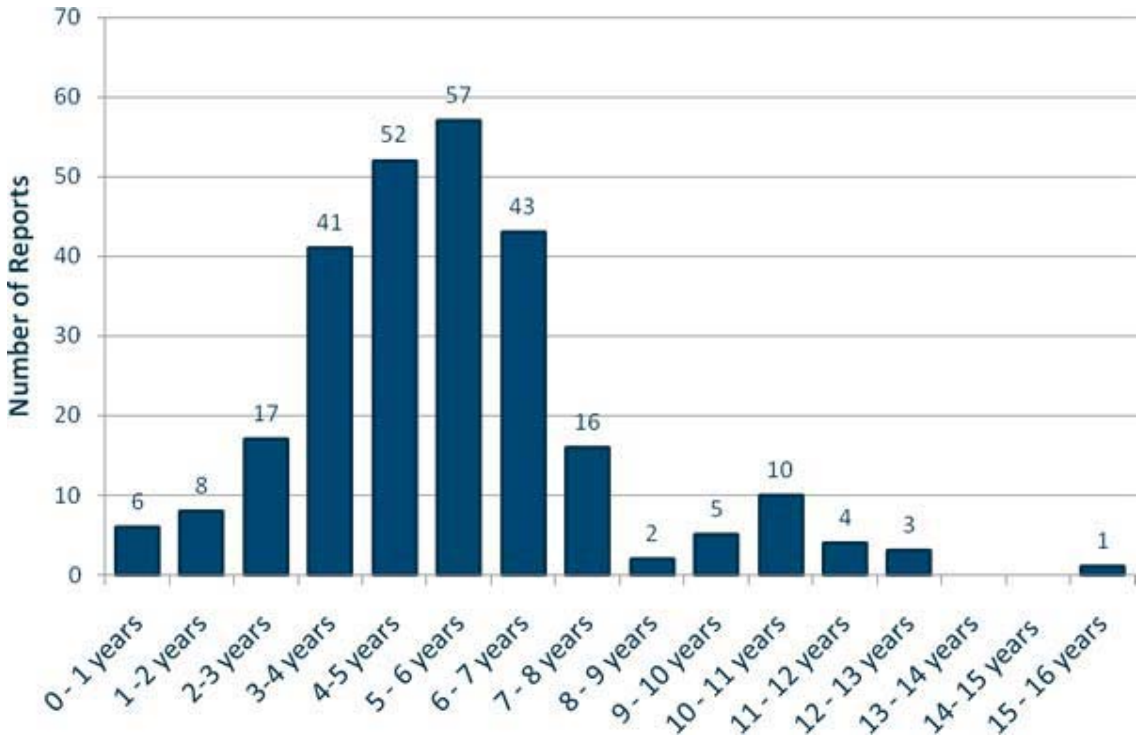

Figure 2. Number of ruptures (at any time after implantation) by year of implantation and % rupture rate by year of implantation as a fraction of implants sold in that year. (PIP implants).

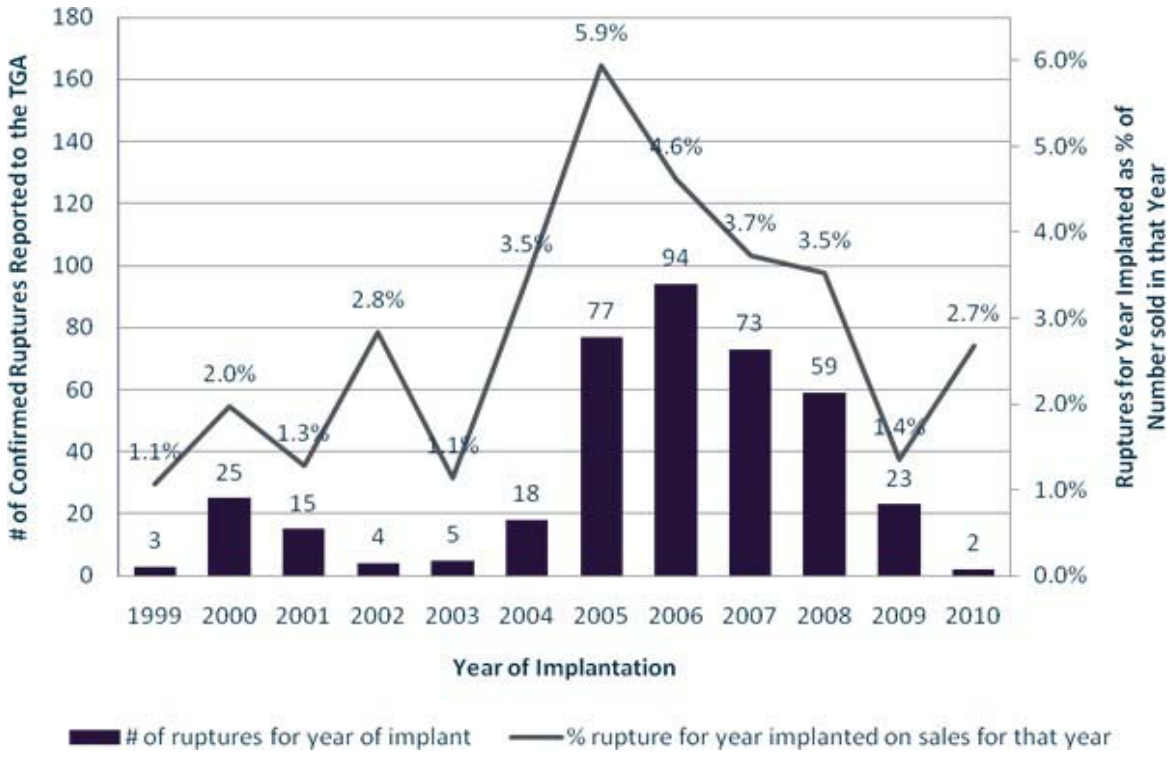

Figure 3. Number of confirmed ruptures for implantation year and as percentage of implants sold in that year.

The above figure shows ruptures for a given year as a percentage of implants sold by the supplier in that year. Being sold in a given year does not necessarily equate to the product being implanted in that year, but it is a reasonable assumption.

The TGA has not published information about local reactions after PIP implant ruptures.

Six Australian women with breast implants have been diagnosed with Anaplastic Large Cell Lymphoma, none of whom had PIP implants. The advice for women with PIP implants is similar to the UK recommendations. Public re-imbursement is allowed for consultations, imaging etc. and/or surgery in case of implant rupture.

Comments on the Australian data:

A limitation of the Australian explant data is that reporting of ruptures increased markedly in 2012 due to a request by the TGA for surgeons to make reports about PIP implants. TGA does not hold comprehensive rupture data for all PIP silicone breast implants including data on ruptured implants that may have occurred prior to the stimulated reporting that occurred in 2012.

It can be concluded that PIP implants were not widely used in Australia and the limited number of reporting probably reflects that. The finding of most ruptures among 5-6 years old implants correspond with the French findings, and also the UK data, where ruptures were evident after 5 years of implantation.

7.2.4. Spanish data

The estimated number of women implanted with PIP implants in Spain is 18 500, and the number of implantations is 37 000 (assuming all implantations as bilateral). Only 4.2% of patients had the implantation in the National Health System (http://www.aemps.gob.es/ - not officially published yet).

The PIP explantation protocol was published on March 2nd 2012. From March 2nd 2012 until March 1st 2013, 2 671 explantation forms were received at the National Centre of Epidemiology of the Instituto Carlos III, Madrid. Explantations were voluntary in private clinics and in the public hospitals where women were referred to in all regions.

A sample of 1500 forms were analysed (56%), recording 2 755 implants. This data is only provided from people with removed implants, and not from the ones not being removed. Therefore, it can result in the overestimation of rupture rate, and the underestimation of the implants surviving rates. In 1037 cases (70%) implants were explanted without previous symptomatology, that is to say, in a preventive way.

In a study of 1 500 people, 376 presented rupture of implants; this means that implants failed in 25.6% of patients. Apart from ruptures (25.6%), the following findings were noticed: changes in the color of filling (15%), contractures (3.3%), calcium accumulation (1.5%), adenopathies (2.5%), inflammation (0.3%), siliconomas (0.7%).

From the 1 037 patients that did not present with symptoms, 70 had ruptured implants, corresponding to 6.8%. Overall, 70 of 1 500 women; i.e. 4.6% had asymptomatic/silent rupture. According to the Spanish data (not shown here), rupture probability was estimated to be 10% in 5 years, which means in 100 patients with implants 10 would suffer a rupture of at least one of their implants during the first 5 years. The possibility of rupture in 10 years was estimated to be 45%, which means, in 100 patients with implants, almost half would suffer rupture of, at least, one of their implants during the first 10 years.

Comments on the Spanish data

The above data reported to the Epidemiology National Center includes the results from a prospective registration during a very recent one-year period. A subset of the reported explantations has been analysed so far. 70% of the explantations were performed for preventive measures, and no symptoms were present. In this subgroup, rupture was found in 6.8% of the women while the overall proportion of women with ruptured implants was 26.9%. As stated above, these figures are probably biased since women with symptoms probably are over-represented among those seeking explanation; but still 70% were operated for preventive measures – a similar proportion as in France. The findings during surgery are also in good concordance with the French data with regard to ruptured implants, but a lower reporting of inflammatory reactions was noticed: adenopathies (2.5%), inflammation (0.3%), siliconomas (0.7%).

A 5- and 10-year cumulative rupture probability, respectively, of 10% and 45% was estimated. These figures are close to results in some of the clinical studies cited below.

7.2.5. Swedish data

In June 2013, the Swedish Medical Products Agency (MPA) presented both clinical and toxicological as well as chemical reports on their homepage including a recommendation of prophylactic explantation for all Swedish women with a PIP implant, even for those who were asymptomatic. These recommendations were an up scaling of previous recommendations (Swedish PIP evaluation).

The MPA sent out questionnaires to the 12 clinics, which had used PIP implants, and to all other aesthetic clinics as well. They received responses from 11 of the 12 plus an additional 3 clinics, where PIP implants were removed. Response rate to specific questions varied greatly and it is cautioned that the results should be interpreted with care.

Summary of the Swedish report

In total, 4 082 women received PIP implants in Sweden between April 2002 and March 2010. The total number of reported ruptures of PIP implants is 102 in 88 women, giving a reported rupture rate in women of 2.2 %. An increased rupture rate cannot be tied to any specific lot numbers, or to any certain year of manufacture of the PIP implants. It has not been possible to identify any group who has an increased risk of rupture of their PIP implants.

The time from implantation of the PIP implants to removal of a ruptured PIP implant was, on average, 38 months. Of the ruptured PIP implants that have been removed, 93 % were removed within 5 years of implantation. The most commonly reported symptoms of a ruptured PIP implant are swollen lymph nodes or lumps in/around the armpit, pain, capsular contracture and a swollen breast. In ruptures for which data were available, about half were so-called, silent ruptures, i.e. without visible or experienced symptoms.

The most common operative findings in cases where it was known in advance that the PIP implant had ruptured were exudate, enlarged lymph nodes and siliconomas, each of which was frequently present (61, 32 and 23 %). These findings were also present in cases of silent rupture, but they were less frequent.

One report indicated not only a very pronounced inflammatory reaction around the ruptured PIP implant, although no infection could be established, but also that there was an inflammatory reaction on the other side where the implant was intact. During operations on ruptured PIP implants with the surface finish "TX", the gel of which had a high concentration of D4, it was observed that there was a higher rate (12/32 = 38 %) of discolored, opaque viscous exudate around the implant, compared with PIP implants with the surface finish "MX" (0/8 = 0 %), the gel of which has a very low or undetectable concentration of D4. Around their PIP implants there was only a thin, clear fluid in the prosthetic cavity.

The Swedish conclusions

In March 2012, the reported rupture rate in women was 1.7 %, which was assessed to correspond to the actual number of women who had, at that point, been operated on and whose PIP implants had ruptures. Since then, additional ruptures have been reported, giving a reported rupture rate of 2.2%. This is assessed to be an underestimation of the actual rate, as there has not been any systematic reporting since March 2012. It has not been possible to identify any groups that are at an increased risk of rupture.

According to the report, PIP implants can cause severe local inflammation. About half of PIP ruptures were reported to have been silent, i.e. did not give rise to any symptoms. Silent ruptures can also show local inflammation, but less frequently. Moreover, PIP implants containing silicone gel of the type containing higher concentrations of D4 (octamethylcyclotetrasiloxane) may cause more severe local irritation than implants with undetectable concentrations of D4.

The Swedish MPA and the Board of Health recommends that clinics, which have implanted PIP implants, should contact the women and inform them about the opinion and the risks in both keeping the PIP implants and in undergoing explantation/exchange surgery. Clinics that have inserted PIP implants should also take them out, even as a prophylactic measure. In specific cases a medical reason may exist for not removing the implants.

Breast implants can cause migrating silicone, which can induce local or regional inflammatory processes. This is not a PIP specific phenomenon, it occurs with all breast implants. The difference with PIP implants is, that some PIP implants (with PIP 2 gel)

contain larger amounts of cyclosiloxanes than other breast implants on the market. One of the cyclosiloxanes, D4, is claimed by the Swedish authority to be a tissue irritant and is considered to cause inflammatory reactions. The Swedish report states that potential long-term effect of a chronic inflammation, induced by D4, cannot be predicted.

A potential chronic long-term effect could be a risk factor for development of cancer, even though this has not been found with PIP implants. It is not possible to point out who has PIP implants with a high level of D4 and who has not. According to the report, there is a risk that the health implications of D4 are underestimated. MPA has performed laboratory analyses and toxicological evaluation and has not found any other substance than D4 as a potential reason for local tissue irritancy. The hypothesis that D4 could be the cause of irritation is substantiated by a study on rats and the clinical picture of a minor group of patients from Swedish clinics.

Knowledge of potential long-term effects of migrating silicone containing D4 is lacking. The majority of PIP implants were inserted during 2005-2010; and long-term data therefore is lacking for observations and retrospective analyses as well as evaluations regarding cancer risk performed by different health authorities. In the MPA evaluation of pros and cons towards prophylactic explantation of PIP implants, it is concluded that in case of a healthy women with no major comorbidity, it is advisable to remove the implants before a rupture happens, since the operation is shorter and easier than the one in the presence of a ruptured implant.

Comments on the Swedish report

The Swedish data are small. It includes findings on a small subgroup of women with PIP implants and only few details are given. We are not informed about the total number of implants reported to the MPA, only how many were ruptured. In about half the cases the rupture was silent. Compared to data from other countries it seems that symptomatic ruptures were overrepresented in the Swedish material, or in other words, the material is somewhat biased towards symptomatic patients, and the overall proportion of rupture is low and in accordance with the UK material. However, as the MPA itself comments, a large underreporting has to be assumed. In ruptured implants, exudate, enlarged lymph nodes and siliconomas were found frequently (in 61%, 32% and 23 %, respectively.) One specific case with gross signs of inflammation seems to have prompted the MPA to recommend prophylactic explantation of all PIP implants. In addition to this case, an evaluation of potential toxicity of D4 was made, primarily based on results from a 1999 paper (Pfleiderer et al, 1999) The Swedish authority conclusion that D4 is an irritant is not supported by a weight of evidence (see section 6).

The Swedish MPA and Board of Health has taken the standpoint that any risk of spread of silicone from PIP implants should be avoided, and explantation therefore should be advised even when specific toxic substances have not been identified.

7.3. Scientific publications on PIP implant

7.3.1. Berry and Stanek (2012)

Berry and Stanek in 2012 reported the results of a follow-up study of 453 patients from a single-surgeon UK clinic. All of them received PIP implants between 2000 and 2005. All patients were invited for a follow-up and those who responded were assessed by ultrasound and, if appropriate, by surgical explantation. The authors reported that 15.9%-33.8% of PIP implants were ruptured (the lower number if not-examined implants were intact and the higher if the proportion of ruptures was identical in the examined as well as not-examined part of the cohort). The authors had operated on 3.5% of the cohort for serious capsular contracture. Three women (0.7%) had

siliconomas, but no signs of inflammation or other complications related to implant rupture were reported. The rate of capsular contracture was not considered to be elevated compared to other implant brands. The author's findings were comparable to those of the UK, French and Australian analyses that ruptures were prominent from about 5 years of implantation time.

The UK expert group (2012) have re-analysed the results of Berry and Stanek with the agreement of the authors. They found that 37% of patients could not be contacted and a further 9% declined the invitation to follow-up. Of the remainder, a rupture was found in one or more implants in 35% of cases. They estimated that the rupture rate at 10 years after implantation could lie between 18% (if assumed that those not followed up were all free from rupture) and, more plausibly, 31% (assuming that these unobserved patients were similar to those with follow up).

A second publication from the same authors Berry and Stanek (2013) has very recently been published. Due to further media attention, 127 patients turned up for follow-up either de novo or for further contact, increasing the total cohort to 460. To date, 283 of 460 (61.5%) have been reviewed of whom 167 have undergone ultrasonography. In total, 163 (35.4%) have had their implants removed or replaced. A ten year PIP implant rupture free survival was estimated using Kaplan-Meier analysis to 60% to 81%, with 95% confidence intervals of 54-67 and 78-85, respectively. (The two estimates represent the two different scenarios outlined above). In other words it can be estimated that 19% to 40% of PIP implants will be ruptured after 10 years of implantation. 31.6%. of the women who came due to the media attention had silent implant rupture and overall, ruptured devices were found in 36.5% of those operated on. Ultrasonography proved very reliable, with a sensitivity of 97.3% and a specificity of 93.1%. More women being examined thus increased the estimated rupture prevalence, even though these had not come forward with symptoms. Still, 32.5% of the cohort has not come forward/been reached despite the heavy media attention, bringing the authors to conclude that some women have a laissez faire attitude towards their implants.

Comment on the Berry and Stanek studies:

The above studies are very important and constitute the second largest series of reporting on PIP implanted women operated in a single clinic and with good or as good as possible follow-up. All attending women underwent clinical examination and 59% of them also ultrasonography, which in this study proved to be a very reliable method to determine implant integrity. Data about implant rupture is therefore very valid and estimates regarding 10-year survival have been calculated including 95% confidence intervals. In contrary to what could be expected the rupture prevalence went up, when additional (reluctant) women were included in the study. A limitation of the studies is that: presentation of the rupture results was somewhat summarily and when the UK expert group re-analysed the figures from the first study, presumably grouping slightly different, came up with almost the same results. The authors only encountered 3 cases (0.7%) of complicated implant ruptures with siliconomas and 16 patients (3.5%) had capsular contracture Baker III/IV (significant or very significant scar tissue around the implant). A large proportion of women had silent implant rupture with no clinical symptoms, which is very reassuring.

7.3.2. Quba and Quba (2013)

Quba and Quba in May 2013, reported on their results from a single-surgeon practice. They present explant data on 338 patients with 676 implants; so far the largest series from one clinic. A subset of 160 underwent ultrasonography before operation and this

was highly efficient for diagnosing rupture with a sensitivity of 90.6% and a specificity of 98.3%. The implants were inserted for cosmetic augmentation in the period 1999-2007 and had a mean age of 7.8 years (range 1-13 years). One hundred and forty four implants (21.3%) were ruptured in 119 women yielding a rupture proportion of 35.2% per patient. 29.4% of patients demonstrated loco-regional spread of silicone to the axilla on scanning, however, only one patient needed removal of lymph nodes.

A statistical difference ($P < 0.001$) in rupture rates between implants inserted prior to 2003 and those inserted from 2003 was demonstrated, with higher failure rates in the latter group (see figure below). The authors think this to substantiate the view that non-medical grade silicone was used in the latter period. There was also a significant difference in rupture rates depending on pocket placement of the implants. Implants were more likely to be ruptured if inserted in the sub muscular plane compared to the sub glandular plane (almost twice as often).

From the paper, the below bar-diagram and table has been copied:

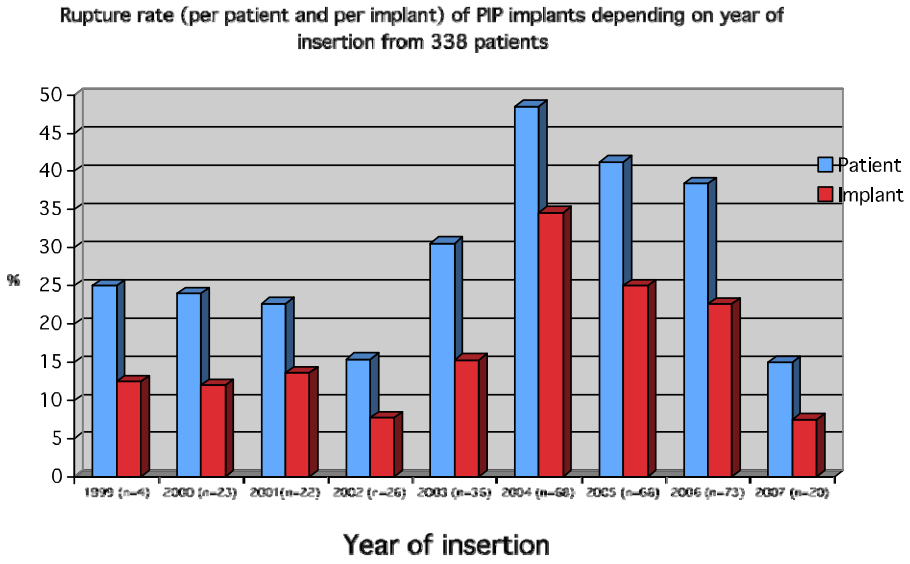

Figure 1 Rupture rate (per patient and per implant) of PIP implants depending on year of insertion from 338 patients.

Table 4 Comparison of rupture rates between sub-glandular and sub-pectoral pocket.

Position of implant	Patients (*n*)	Observation period (years)	Rupture rate/patient (%)	Rupture rate/implant (%)[a]
Sub-glandular	145	8.1 (range 2–13)	26.2	14.8
Sub-pectoral	193	7.5 (range 2–12)	42.0	26.1
Overall	**338**	**7.8 (range 1–13)**	**35.2**	**21.3**

[a] $P < 0.001$ (chi square value 12.698) for rupture rate per implant between sub-glandular and sub-pectoral position.

Table 9: Comparison of rupture rates between sub-glandular and sub-pectoral pocket

Comment on the Quba and Quba study:

This large and strictly reported study confirms the high rupture proportion of PIP implants with figures very close to the other clinical studies mentioned in this section. It also adds important new evidence that implant durability has changed over the years; implants from before 2003 had half the rupture risk of those after, even with a longer

follow-up; presumably due to the manufacturing process and perhaps the introduction of non-medical grade silicone, although this is speculative. Interestingly, it was also found that implants in the submuscular position had an almost double risk of rupture compared with subglandular placed implants. Previous reports concerning other brands of implants have been somewhat contradictory, with some finding more ruptures among subglandular implants (Feng 1999) and others more with the sub-muscular position (Brown 2000, Hölmich 2001). It can be speculated that the continuous movement of the pectoralis muscle will induce wear-and-tear cracks in the implant membrane being responsible for the higher number of ruptures in implants in this position. It is noteworthy, that inflammatory reactions were not reported, besides accumulation of silicone in regional lymph nodes in about a quarter of the patients. This was closely associated with implant rupture, but only in one case was symptomatic so that the patient had to be operated for the condition.

7.3.3. Maijers and Niessen (2012, 2013)

Maijers and Niessen (2012, 2013) have published two reports about their PIP experience in a Dutch private clinic. All women (n=475) operated on, for cosmetic breast augmentation with PIP implants during 2000 and 2001, were invited for a clinical examination. One hundred and sixty five women came for a follow-up visit; of which 112 were eligible for inclusion in the study, which comprised a clinical examination and an MRI examination. Data from the first study include findings from the MRI showed that at least one implant was found ruptured in 37 of the 112 women (33%), the mean implant age was 112 months (range, 111-133 months) and all implants were round textured PIP implants. The 10-year point prevalence of rupture was 24%. There was no difference in the proportion of ruptured implants from 2000 and 2001!

Twelve of the 112 women had physical signs of rupture (asymmetry, palpable node in axilla, change in form, size or consistency), but rupture was only found in half of these cases at MRI. Of the 100 women without symptoms, rupture was found in 31. The authors concluded that the examined PIP implants have higher rupture prevalence than comparable newer implants, which have reported rupture prevalences around 8-17% after about 10 years of follow-up, but are comparable to the rupture prevalences found among older implants.

In the subsequent study (Maijers and Niessen, 2013) on the same cohort, all women with at least one ruptured PIP implant were offered surgery. This study reports on the findings at surgery. Thirty-four of the 112 women (30.4%) reported pre-existing symptoms in 54 implants (33.7%). Complaints mentioned were pain or burning sensation by 20 women and changed size, form and/or consistency of the implant in 9 women. Four women had a palpable mass in their breast or axilla. None of the symptoms had led them to ask for consultation at the clinic. Of the 171 implants in which the women reported no preexisting complaints, MRI found a rupture in 40 implants (23.4%) compared with 14 (26.4%) in the symptomatic group.

Thirty-seven women with at least one ruptured implant were offered explanations. A sensitivity of 89.7% and a specificity of 51.9% of the MRI results were found. A milky colored fluid was also found with some ruptured implants, and a change in gel-consistency and color was typically noticed in cases where the shell was ruptured. Capsulectomy was performed in 10 women, and the tissue was examined histologically. Fibro-adipose tissue with histiocytic reaction, silicone deposition and in one case giant cells were found. There was no case of malignancy and no cases of bacterial growth.

Comments on the Maijers and Niessen studies:

The above studies by Maijers and Niessen are very valuable. It is noted that they found a high prevalence of PIP implant ruptures, both among implants inserted in 2000 and 2001, however, the women with implant ruptures were not more likely to have symptoms from their breast than those without ruptures. Besides ruptured implants with sometimes almost disintegrated membranes, no unexpected finding was identified during surgery. Although some women had symptoms such as a burning sensation or pain in the breast, this was only in half the cases associated with implant rupture and most ruptures were found in asymptomatic women.

These studies were conducted in a rigorous way and performed before the large media attention on the PIP implants. The results are therefore likely to be pertinent. The major limitation is that the majority of invited women could not be reached and/or had decided not to participate. As in other similar studies it is however not likely that women with the most serious symptoms would be the ones deciding not to participate in a follow-up study of this nature. However, the women who had had their implants removed at other clinics prior to the study would not be eligible to participation, and this could skew the study population towards healthier patients.

MRI validity, in specific specificity, turned out to be lower than in most other recent studies, however, this may be explained by a large proportion of implants with heavy gel-bleed which came out as false-positives. Clinically, this was probably not a problem, since a device with a large amount of gel-bleed could be perceived as almost as failed as a ruptured implant. In addition, as the authors rightly point out the previous MRI studies have in most cases dealt with less cohesive gel implants, where the rupture diagnosis could be expected to be easier and no study has evaluated the precision in the very cohesive gel implants; i.e. contoured implants.

The findings of the Dutch studies are in very neat concordance with the above-mentioned UK studies. If implants before 2003 are indeed more solid as suggested by Quba and Quba, this Dutch cohort represents a sample of the more solid PIP implants – with about one-fourth ruptured after about 10 years of implantation.

7.3.4. Other studies about PIP implants

Chummun and McLean (2013) have just published their experience with a cohort of 49 UK patients operated on with PIP implants during the period 1999-2008, with most (n = 24) of the surgeries performed in 2005. Five patients declined follow-up. Of the remaining 44 patients, 35 were asymptomatic, 2 patients had a Baker III/IV capsule. Four patients (9%) had axillary lymphadenopathy, which were shown to be silicone lymphadenitis. One patient presented with a breast lump and one patient complained of breast pain. One patient had an 800-ml seroma at the time of examination. Thirty nine patients wanted explantation; 18 because of anxiety and 15 because of silent rupture found at scan, the remaining had symptoms: 3 considered that they had an aesthetic change in their breast appearance, 2 complained of palpable axillary node and one patient had a breast lump. At explantation, 61 implants were not ruptured and 17 were ruptured, comprising a rupture rate of 21.8% after a mean follow-up time of 7 years. 15 of the 17 ruptures were asymptomatic. Among the 61 non-ruptured implants, 22 implants had a yellow colour, 41 had mild gel bleed, 1 moderate gel bleed and 1 severe gel bleed. Two of the ruptured implants had a simple tear, while the remaining 15 were totally disintegrated. The gel had retained its cohesive nature in 3 cases, while reduced cohesion was found in 10 cases; in one case the gel was liquid. The fibrous capsule was noted to be normal in 70 cases, and inflamed in 6 cases (7.7%). Two patients had severe capsular contracture. Biopsy of the 6 inflamed capsules showed silicone granuloma in 2 cases, and non-specific inflammatory cells in the remaining 4 cases.

This smaller study is in line with those discussed above although inflammation seems to have been encountered slightly more often in this patient population.

Cohen-Tervaert and Kappel (2013) identified from their clinic of patients with autoimmune diseases, 32 patients who also had silicone breast implants. They diagnosed these women to be suffering from silicone implant compatibility syndrome and autoimmune/inflammatory syndrome induced by adjuvants. The authors' argument that some patients can become allergic to silicone, and this may happen years after implantation since it occurs only when free silicone has migrated in the body beyond regional lymph nodes. In 17 of the 32 women, a systemic autoimmune disease was diagnosed and in 15 of the 32 patients, an impaired humoral immune system was found, presumably because free immunoglobulin adheres to the implant shell. The main theories put forward in this paper are not new and have been extensively discussed and tested in large epidemiological studies, without any study being able to substantiate these theories. Once appropriate control groups have been included, no excess of neither regular CTD nor uncharacteristic rheumatic disorders have been found. However, it is methodologically not possible to draw conclusion from large-scale studies to individuals. If an association exists, it must be so rare, that it could not be found in large well-designed epidemiological studies. The relevant studies were discussed in the first SCENIHR report.

Reyal et al (2013) reported on findings from the Institut Curie where PIP implants were used widely in the period 2001 -2011. Of 915 breast cancer patients who were operated on for breast reconstruction with PIP implants; 715 patients were analysed. No information about the remaining 200 patients was given. Most of the patients (n=585) had immediate reconstruction, 120 had delayed reconstruction and 190 had delayed contralateral symmetrisation procedure, while this was done immediately in 70 patients, many patients were operated on several times with sequential procedures as part of the reconstruction, but also for improvement or due to complications.

From 2002 to 2009, the median number of removed PIP implants was 32 per year (range, 8-41). Before 2009, aesthetic improvement was the main indication, but since

2010 having a PIP implant itself was a reason for re-operation in 75% of the cases. Implant rupture was only reported in less than 5% in implants removed during 2001-2007, increased to 8% in 2008 and 14% in 2009. In 2010 and 2011, the proportion of ruptured implants was 20 and 23 percent, respectively.

The authors suggest that reconstruction patients constitute a different study group from cosmetic patients and that the different environment that the implant is harbored in could have an impact on durability. This is somewhat speculative, since this phenomenon has never been investigated, and the proportion of ruptured implants does not differ from previous reports. The study is interesting however since it is a very large cohort of reconstructed patients and it has obviously not been easy to get the data for reporting due to the several re-operations. However, crucial information about implant age at rupture/explantation is missing. A Kaplan-Meier implant survival plot would have been very illustrative and made comparison with other studies much easier and straight forward and the data for performing this analysis must be at hand.

Additional French studies have been reported. Based on the English abstract, the below information has been obtained: Crouzet et al (2012) also reports on breast reconstruction patients from a public hospital. From 2006, 128 anatomical/asymmetrical PIP implants were used in 116 patients. Sixteen percent of implants were removed before the PIP breast implant crisis and none of these were ruptured. Since then, 61.2% of the patients have been re-operated and 76 (59.4%) of implants removed. Ten implants (13.1%) were abnormal; three of them (3.9%) were ruptured. Six implants

(7.9%) had gel-bleed. The average life span of the PIP implants in situ was 21.3 months. Three postoperative complications were observed among the operated patients. It is noted that the number of implants with rupture or other malfunction was somewhat lower than in the above-cited studies. However, since the PIP implants were only used after 2006, this is to be expected, and a proportion of malfunctioning implants of 13.1% is higher than in most other studies.

Based on the rather few findings in the European questionnaire it seems that ruptures were more frequently reported in implants inserted before 2006, and this may be consistent with the change in manufacturing, since the TX or micro texturing was introduced around that time. These membranes have in a German study proven more resilient than the textured or smooth membranes (Walter 2012, Schubert et al 2013) (see appendix 1). Aktouf (2012)) evaluated 99 patients with 192 PIP silicone breast implants for breast augmentation; 184 were textured and 8 were smooth. The implants were implanted in the period 2005-2010. All patients underwent a clinical examination and an ultrasonography. MRI was used in cases of doubt. They found 23 ruptured implants (12%): 18 intracapsular and five extracapsular in 17 patients (17.2%). They also found 28 patients with axillary lymphadenopathy and eight with loco regional silicone spread (36.4%). 35 patients (35.4%) had chronic breast pain. The authors conclude that their study supports the decision to withdraw all PIP silicone breast implants. It should be emphasized however, that this study reports findings at clinical and imaging examination not from surgery and therefore imaging precision was not evaluated. A high number of ruptured implants were found and even more implants showed signs of silicone migration. All implants were younger than 5-6 years of age. A large proportion of the patients had breast pain, however, only a small number choose surgery at the time of study.

Carillon et al (2012) evaluated 31 breast reconstruction patients with 33 PIP implants between 2006 and 2010. The mean implantation time was 15.35 months. Eight implants were removed, three of these were with intracapsular rupture and 2 of them were symptomatic. Most of the patients at this centre opted for surveillance rather than surgery. 9% ruptured implants is an estimated minimum figure, since only eight implants were removed. This is however a huge number bearing in mind the short median implantation time.

A Greek study (Zambacos et al 2013) reported 14 cases of silicone lymphadenopathy after breast augmentation, ten of which were with PIP implants. The authors also carried out a literature review of this subject. They identified 29 reports involving 175 cases of silicone lymphadenopathy, of which 164 had usable data. They presented data stratified into two time periods: before and after the year 2000. Release or migration of silicone into the surrounding tissues invokes a straightforward, nonspecific foreign body reaction, resulting in typical macrophage invasion, giant cell formation, and eventual scarring. Silicone lymphadenopathy is simply a deposition of silicone in one or more lymph nodes due to lymphatic migration of silicone and represents a normal physiological response to the presence of foreign material. Silicone seems to be phagocytized by multinucleated giant cells. When silicone lymphadenopathy occurs, it is generally a rather late finding, 6-10 years after implantation, and the large majority of cases from the literature were before and including 2000, however 15 cases were after 2000; 12 of which had received PIP implants. In their own 14 cases, all but one was found with leaking or ruptured implants. The diagnosis was either clinical or found incidental during ultrasonography or mammography. They conclude that improved implant technology has decreased the occurrence of lymphadenopathy, although there is no knowledge of the incidence and prevalence in the literature. They also conclude that breast implant removal is not warranted unless symptomatic or if it interferes with breast cancer diagnosis or treatment.

7.3.5. Additional unpublished data

The SCENIHR had access to data from one private Brazilian practice, kindly provided by Dr. Sanabria, through the International Conference for Plastic Reconstructive and Aesthetic Surgery (IPRAS): In 495 women with 990 PIP implants, 49 implants were found ruptured, corresponding to 5% in 9.9% of the women. In 7 cases, regional lymph nodes were observed, and in 9 implants, capsular contracture was noted. A survival analysis based on the first 341 women found an estimated 10-year implant survival of 84%, corresponding to 16% of implants being ruptured at 10 years of implantation. All fibrous capsules in ruptured implants have been sent to histological examination and no pathology was found. In about one-third of ruptures, an axillary lymph node was sent for histology and chronic inflammation was found.

The data from this Brazilian clinic represent a large series of explanations. However, not many details have accompanied the raw data. It is evident that implant ruptures also occurred in the South American PIP implants, but presumably in lower numbers than reported in the European studies. The calculated survival curve corresponds to what would be expected from other third generation implants.

7.3.6. Case reports about unusual complications in patients with PIP implants

An increasing number of case reports with PIP implantation and primarily significant clinical adverse reactions have been published recently. A common reporting is serious inflammation within the implant pocket, thickened fibrous capsule, enlarged and silicon containing regional lymph nodes – both in the axilla and neck region. For a summary of these findings, please go to appendix II.

7.4. Specific conditions

7.4.1. Update on Anaplastic Large Cell Lymphoma (ALCL)

In May 2013 case reports of 130 patients, who developed Anaplastic Large Cell Lymphoma (ALCL) in the capsular tissue around the implant, are documented (Aladily et al, 2012 a and b, Taylor et al 2012, Taylor et al 2013, Largent et al 2012, Mychaluk et al 2013, Zakhary et al 2013). Among these 130 cases 4 patients had received PIP implants. In 1 out of these 4 patients the course of this disease was lethal. It can be concluded from these data that this is of no statistical relevance.

7.4.2. The psychological impact of the PIP implant "scandal"

In the UK a cohort study with 100 patients who had received breast implants for breast reconstruction after breast cancer was performed. The manufacturers of these implants were not specified. In 92% of these patients the media coverage of the PIP scandal had 'some impact' on their lives, in 32% this impact was 'powerful' and in 9% the impact was 'severe'. (Segaren et al 2012). Although the media coverage is a particular cause of psychological impacts other factors may also contribute.

7.4.3. Update on breast cancer detection

Lavigne et al. (2013) have carried out a systematic review and two meta-analysis of

studies about breast cancer diagnosis in breast augmented women. They conclude that having a breast implant for aesthetic reasons has an adverse effect on the survival of women who are subsequently diagnosed as having breast cancer; presumably because of difficulties in detecting and diagnosing the cancer. Women with breast implants for aesthetic indications had later stage tumors at diagnosis of breast cancer and the breast cancer specific mortality was increased in women with breast implants for aesthetic indications.

The authors warn that the findings should be interpreted with caution, as some studies included in the meta-analysis on survival did not adjust for potential cofounders. They state that further investigations regarding diagnosis and prognosis of breast cancer among women with breast implants are warranted.

7.4.4. Update on capsular contracture

Since the preparation of the first Opinion, two recent papers published in 2013 have confirmed the hypothesis of a link between a biofilm, surrounding the breast implant, and contracture. Previous papers (Pajko 2003, Schreml 2007) described the presence of coagulase-negative staphylococci, mainly species of staphylococcus epidermidis group, significantly associated with capsular contracture, without significant difference of culture positivity for saline versus silicone implants or smooth versus textured surface. However, there was a significant difference in the degree of contracture. According to Schreml et al., the difference in colonization between Baker I/II and Baker III/IV contracture was highly significant ($p<0.001$). In the paper of Rieger et al. (2013) cultures after explantation without clinical sign of infection were performed with the aid of sonication, a more sensitive method than swabbing. This detected mostly skin bacteria like propioni bacterium and coagulase negative staphylococci. The grade of contracture and the implant culture rate were highly correlated ($p<0.001$), but the authors did not give information about the type of implants removed. This paper did not confirm the probable link between biofilm formation and the type of implant's surface (smooth vs textured) as previously described by some authors (Malata 1997, Wong 2006, Hvilsom 2009). However, the recent work of Valenzia-Lazcano et al (2013) demonstrated that textured surfaces show less contracture than smooth surfaces by restricting the influence of fibroblasts. Additional research performed on artificial surfaces (not breast implants) has pinpointed the role of micro/nano-textured surfaces in slowing down the attachment (adhesion) processes (Machado 2010). Based on the available evidence it would appear that there could be a link between a biofilm surrounding a breast implant and contracture. Textured surfaces could cause less contracture than smooth surfaces as a consequence of restricting the influence of fibroblasts.

Based on the reports of capsular contracture in PIP implantation from the UK, the French, and the Spanish studies as well as the clinical studies, capsular contracture in PIP implantation does not seem to be excessive compared to other implants as mentioned before in discussion of the French data. It is not possible to evaluate, whether capsular contracture was less frequent in the textured than the smooth PIP implants, since most studies do not include information about PIP implants in detail.

8. OVERALL CONCLUSIONS

8.1. Ruptures

All the above cited reports and scientific papers show that PIP implants produced in the period 2001-2010 have a higher probability of rupture and also of earlier rupture than other breast implants. Other implant brands from 3rd and 4th generation and from the same production time have an estimated probability of rupture of 2-15% within 10 years of implantation (Heden 2009, Collis 2007, Hölmich 2001, Hölmich 2003) see table in Appendix III for details. From the UK expert group data it appears that PIP implant ruptures occurred 2-6 times as often as with implants from other manufacturers. From the UK, the French, and the Australian data it appears that implant ruptures can occur after only a few years of implantation and that a median implantation time until diagnosis of rupture and explantation of 5-6 years is common in the clinical setting. The French ANSM report 16.6% of implants to be ruptured at the time of explant surgery (after a median implantation time of 5.9 years).

The studies by Barry and Stanek and by Maijers and Niessen add significantly to the general picture since both groups have presented 10-year cumulative rupture risk. In the British studies it was found that 19% to 40% of PIP implants can be estimated to be ruptured after 10 years of implantation (Barry and Stanek, 2013). In the Dutch studies, a 10-year point prevalence of rupture was 24% (Maijers and Niessen, 2013).

The study methodology was not comparable for several reasons; one being that implants were evaluated with ultrasonography in the British studies and with MRI in the Dutch studies; the former surprisingly being more precise for this type of implant. It is worth noticing that the Dutch study included implants from 2000; the French authorities have announced that the problems with PIP implants concerns implants produced in 2001 and onwards. Proportion of ruptures in the Dutch 2000 PIP implants were comparable to the 2001 PIP implants, which could indicate that also so called 'regular PIP implants' also had a rather high number of ruptures. No other study or report has looked into this.

Other clinical studies substantiate these findings: Quba and Quba found 21.3 % ruptured implants after a median of 7.8 years, Chummun and Maclean almost identically found 21.8% of implants ruptured after a mean follow-up time of 7 years. The other clinical studies are smaller and with shorter implantation time and thus not so informative.

In the UK report, significant gel-bleed was included in the group of device failures and it was not reported how many of the failures were actual ruptures and how many were significant gel-bleed. In the French ANSM report, malfunctions besides rupture included gel-bleed, which was found in 6.8% of explantations. Crouzet also described this in a French study, where 7.9% of implants showed gel-bleed. Chummun and McLean found 41 of 61 not-ruptured implants with light gel-bleed, one with moderate and one with severe gel-bleed; in total in 70.5% of not-ruptured implants or in 55.1% of all removed implants. In the Dutch study (Maijers and Niessen, 2013), gel-bleed accounted for half the number of false-positives. Gel-bleed was not mentioned in in the Australian TGA reporting.

For an overview of the different rupture studies on both PIP implants and non-PIP implants, please see table in appendix III.

8.2. Adverse effects/inflammation

Adverse effects due to free silicone and/or gel-bleed in the form of siliconomas, lymphadenopathy, lumps etc. have been reported less uniformly than implant ruptures. In the report from the UK expert group, the conclusions regarding this subject were: PIP implants are 3-5 times more likely than other implants to result in local clinical signs. The rate of explants with local clinical signs is 0.8% at five years rising to 2.1% at 10 years. PIP implants are not associated with higher risks of other clinical problems such as capsular contraction, haematoma or cancer.

In the French ANSM report the proportion of adverse events with PIP implants was 16.6% per breast (4 257/25 644) or in 18% of the study women. If capsular contracture is subtracted, the figure is 8.8% per breast (2256/25644) or 15.3% per woman. In the British reports by Berry and Stanek, the aspect of clinical complications was not prominent. The authors had operated on 3.5% of the cohort for serious capsular contracture, three women (0.7%) had siliconomas, but no other signs of inflammation or other complications related to implant rupture were reported.

In the Dutch studies by Maijers and Niessen (2012, 2013), 3 women (2.7%) had palpable lymph nodes in the axilla, and in half the cases this was seen with a ruptured implant. The capsular tissue in 15 implants (6.7%) could be classified as Baker III and one as Baker IV capsular contracture. This corresponds to a rate of capsular contracture of 7.1% per breast within 10 years, which is within normal range (FDA Update on the Safety of Silicone Gel-Filled Breast Implants). There were no reports of inflammation found during surgery. In the study by Chummun and McLean, two patients out of 44 had Baker III/IV capsule (4.5% pr. patient) and lymphadenopathy was observed in 4 patients (9%), which was found to be silicone lymphadenitis. They described an inflamed fibrous capsule in 6 cases (7.7%).

In the French study by Aktouf et al (2012) a high number of symptomatic patients was found: 28 of 99 patients with cosmetic PIP implants had axillary lymphadenopathy (28.3%) and 8 (8.1%) patients showed loco-regional silicone spread and 35 patients (35.4%) had chronic breast pain. The abstract does not contain detailed information about histological findings.

In the Greek study of lymphadenopathy (Zambacos et al 2013), histological findings in the cases with PIP implants do not differ from histological findings in cases with other implants. The only difference reported was that the majority of newer cases were seen with PIP implants, and the authors outline that lymphadenopathy was found more often with former generations of implants with higher risk of rupture. Inclusion of a barrier-layer to reduce gel-bleed also reduced the risk of silicone migration to regional lymph nodes etc. Somewhere along the line of production, the PIP manufacturer abandoned this barrier-layer.

As reported in the 2012 SCENIHR opinion on PIP implants (page 35), local complications among silicone breast implant recipients generally range between 17% - 36%, and for instance in the FDA core study on Allergan implants, 15% of study women had capsular contracture after 6 years of implantation (Spear et al 2007). In a parallel study on Mentor implants, 8.1% of women had significant capsular contracture after 3 years of implantation (Cunningham and Mcue, 2007). The probability of capsular contracture generally increases with increasing implantation time (Handel et al 2006, Hölmich et al 2007).

Numbers for lymphadenopathy and siliconomas (7.6%) are difficult to compare to similar populations with relatively short-term implantation, since this has not been reported consistently. In a study of long-term results, 21% and 6% of women had bilateral and unilateral axillary lymphadenopathy, respectively, 2% had silicone granuloma after a mean of 19 years of implantation. (Hölmich, 2007) In another study also primarily involving first and second generation implants, regional lymphadenopathy was found

with 25% of implants, equally distributed among ruptured and intact implants. Median implantation time in that study was 16 years (range, 6-27 years) (Hölmich, 2005).

The case-studies included in this review all report on loco-regional spread of free silicone resulting in several enlarged lymph nodes with silicone aggregation, giant foreign body cells etc. A case of cutaneous affection was also reported, where granulomatous inflammation in the skin, but no silicone, was found. These reports do not add much new information to that reported previously. Similar case reports were predominant during the late eighties and first half of the nineties where second generation implants with very high rupture rates were in use (this resulted in the FDA ban on silicone gel filled implants, and presumably prompted the manufactures to produce more solid implants). However, such reports are still published: Dragu et al. 2009: 6 unknown implants more than 10 years old, Gundeslioglu et al. 2013: one unknown implant six years of age, and Maricevich et al. 2012: one Mentor Siltex Becker implant 15 years old.

It is noted that the study by Barry and Stanek (2006) discussed above was performed before the large media interest as was the Dutch study by Maijers and Niessen) and this could very well have an impact on the subjective symptoms reported by the patients. In subsequent papers it needs to be considered that the authors could be more focused on describing local inflammation once their attention has been drawn towards this issue. It is also noteworthy, that no reports of this nature have been gathered from the Australian TGA and that the Spanish data only contain very few reports of inflammation. The Swedish reports focus on the inflammation issue caused by PIP implants, but this is based on few actual cases.

There is thus some, however conflicting, evidence, that more women with PIP implants have experienced signs of loco-regional inflammation than women with other kinds of breast implants. The differences in the reported symptomatology are most likely due to a reporting bias; but differences in the PIP implants in different batches cannot be totally excluded. However, the UK expert group found no differences in chemical composition in implants from different batches (MHRA 2012). It could also be speculated that a difference in the individual susceptibility could account for the varied picture. This is not very likely, since the variation is among studies, which should mean that for instance French women were more at risk of developing swollen lymph nodes than UK women.

8.3. Overall conclusions on the risks in PIP implantation and explantation

In the case of PIP implants, early implant ruptures are predominant and 10-year implant survival is at the level of second generation implants from other manufacturers.

The PIP implant contents have also been cited by a number of surgeons as having the consistency typical of second generation implants.

The risk of implant rupture increases with implantation time, and can be estimated to be around 25-30% for PIP implants at 10 years of implantation.

Some cases of implant gel-bleed or rupture are associated with an inflammatory reaction locally or in the regional lymph nodes. This was also well-known and described with former implant generations of other brands.

Neither implant rupture nor local inflammation has been found to be associated with breast cancer or the rare anaplastic large cell lymphoma.

The gel from PIP implants with non-medical grade silicone contains more short-chained silicone molecules in particular D4, D5 and D6 than is the case for implants from other manufacturers. It has not been possible to identify any other substances, which differ from implants with medical grade silicone. However there is no convincing scientific

evidence that the amount of siloxanes, which can be found even in implants may cause inflammation in the human body.

Despite the uncertainties regarding the actual risk to individual patients and in view of the public concern, it may be considered advisable for women with PIP implants to be offered regular assessments. This could include: clinical examinations, individual counselling, and/or imaging with ultrasonography or MRI.

Concerning generic risks and benefits of removal of PIP implants, explantation, with or without implant exchange, carries less intra- and perioperative risks if the implant is intact rather than ruptured. Any kind of surgery and general anaesthesia does, however, entail risk of complications as outlined in 2012 SCENIHR PIP implants report. Considering the high rupture rates, however, the vast majority of women with PIP implants will experience rupture within their life span and then will be subject to both: the higher intra and postoperative risk associated with the ruptured implants and the general risk of complications due to surgery and anaesthesia.

There is general agreement among plastic surgeons that, in case of implant rupture and/or if loco-regional inflammation or lymphadenopathy is found, explantation is advised as precautionary measure.

There is currently no convincing medical, toxicological or other data to justify removal of intact PIP implants as a precautionary approach. Implant removal in the absence of malfunction may be considered for women who are experiencing significant anxiety because they have a PIP breast implant. However, the decision to remove an intact PIP implant for this reason should be based on an individual assessment of the woman's condition by her surgeon or other treating physician after consultation.

9. RISK ASSESSMENT

9.1. Risks to the women with PIP implants

Weight of evidence analysis of the animal toxicology data shows that D4 and D5 siloxanes have very low irritant potential. This finding mirrors the situation in patients where leakage or rupture of a PIP implant appears often to be without marked irritancy. The clinical data do not provide good evidence that the adverse effects of a PIP implant rupturing are significantly greater than is the case for the rupture of an implant from another manufacturer. It is also noted that ruptures can occur with no apparent clinical consequences.

Chronic toxicity studies also indicate low toxicity of D4 and D5 siloxanes.

The main effect of interest in terms of risk assessment is the uterine adenomas, which were observed only at high dose levels (inhalation doses of 700ppm D4 and 160ppm D5). Neither D4 nor D5 are genotoxic and it is therefore highly likely that for both D4 and D5 the mechanism involved is a non-genotoxic one and that there is a threshold for the development of the uterine adenomas. Moreover as noted in section 6 the mode of initiation of these adenomas is believed not to be relevant to humans.

It is also pertinent to compare the relative blood levels attained in patients with breast implants with those arising in rats at levels that provoke the uterine adenomas. For D4 and D5 the adverse levels in blood and fat are of the orders of magnitude higher in rats when compared to women with SBI. In addition, in these rat studies D4 is anticipated to be much more bioavailable than in any of the release scenarios following implant failure. Taken together, these findings indicate that release of D4 and D5 as a consequence of a leaking or ruptured PIP implant is unlikely to result in adverse health effects.

On the basis of the available evidence it can be concluded that exposure to siloxanes resulting from the rupture of PIP implants is not associated with any increased health risks.

9.2. Risk to the children of women with PIP implants

9.2.1. Impacts on the foetus

Based on both one and two generation studies there is no evidence that the cyclic siloxanes cause developmental toxicity, or have an adverse effect on rat fertility. Taken in conjunction with the bioavailability and other considerations discussed above it can be concluded that no risk, due to the release of D4 and D5, is anticipated.

9.2.2. Nursing infants

Low levels of siloxanes in breast milk have been found in a single subject with a ruptured PIP implant. However, siloxanes have been found at detectable levels in over 20% of breast milk samples taken from women without breast implants. Moreover, commercially available semi-skimmed cow's milk was found to contain considerably higher levels of total silicone than the sample of breast milk taken from women with a ruptured PIP implant. Thus, no identifiable increased risk for the nursing infant is anticipated from breast milk from a mother with ruptured breast implants.

9.3. Uncertainties in the risk assessment

The two main uncertainties are;

- Other siloxanes are also present in addition to D4, D5 and D6. The toxicological data on these other siloxanes are very limited. In some irritancy studies a mixture of siloxanes was assessed and the irritancy potential was found to be very low. Nonetheless there is no reason to suppose that other cyclic and linear siloxanes will be more potent or show other toxic effects.

- The data are insufficient to provide a good understanding on the degree of variability and the causes of inter-individual response to material released from a damaged implant.

10. OPINION

10.1. The tasks

The following tasks were asked of the SCENIHR:

1. To collect, compile and analyse the data collected;

2. To contribute to the creation of an EU questionnaire to be used for the collection of data on implanted patients;

3. To update the previous SCENIHR scientific opinion on the safety of the PIP silicone breast implants.

4. To provide guidance on the testing undertaken by the Member States in terms of tests and studies to be performed, test methodologies, uniform data production.

The Committee identified a need to:

i) Obtain reliable data on the incidence of breast implant failure not only of PIP devices in different countries;
ii) Identify the physicochemical factors that might influence breast implant failure in particular the influence of the implant contents and the degrading properties of the shell;
iii) Examine whether the adverse effects of a PIP implant failure differ qualitatively and/or qualitatively from those of breast implants from other manufacturers
iv) Characterise important knowledge gaps;
v) Further reduce rupture risks by improved design of breast implants.

The silicone *Poly Implant Prothèse (PIP)* have been produced in France since 2001 in its present form. These PIP silicone breast implants have been found to contain non-medical grade silicone and have thus not been produced according to the documented procedures provided to obtain CE-mark. They have been available in smooth and textured variants as well as round and anatomically shaped. In addition to the brand name PIP, these implants have also been marketed by other companies under the name M-implants, Rofil implant, and TiBreeze. It is estimated that worldwide about 400.000 women have received these implants.

Since the publication of 2012 SCENIHR opinion on PIP implants, more data has become available, especially very recently. In order to include as much as possible in this evaluation, the publication of the present report had to be postponed from the originally proposed deadline.

10.2. Incidence of implant failures

The main factors that contribute to breast implant failure are:

- The physicochemical properties of the implant;
- the mechanical properties of the shell of implants;
- The quality of the surgical procedure for implantation;
- The ageing of materials following implantation.

Silicone breast implants may fail, regardless of manufacturer, and the probability of failure increases with time since implantation. Based on UK data, PIP implants have been found to have ruptured about 2-6 times as often as four other brands of implants commonly used. Based on clinical studies of PIP implants, the probability of rupture can be estimated to be around 25-30% for PIP implants at 10 years after implantation and with many ruptures occurring or being diagnosed after about 5 years of implantation. Other breast implants from the same calendar time have been found to have an estimated probability of rupture of 2% - 15% after approximately 10 years. Clinical findings show that PIP implants behave like second generation implants from other manufacturers.

Mechanical, physical and chemical testing has not revealed any significant deviations from requirements of established safety standards. However, the tests did reveal a great deal of differences within implant and between implant variation in the measured properties. This variation alone may explain higher rupture rates.

10.3. Toxicology of PIP implants

The silicone gel comprises polymeric material with a wide range of molecular weight including the low molecular weight cyclic siloxanes. There is no new data on either the toxicokinetics or the adverse effects of the polymeric material. Batches of PIP implants have been found to contain higher amounts of these siloxanes compared with those of other manufacturers, in particular cyclic siloxanes D4, D5 and D6. It is important to note that all individuals, regardless of whether or not they have had a breast implant, will have measurable levels of D4, and D5 in their blood and tissues as these chemicals are widely used in consumer and household products.

Thorough analyses of PIP implants have failed to detect any other components or contaminants of relevance. Thus the questions that need to be addressed are:

- Do PIP implants represent an increased risk to human health compared with conventional medical grade implants?
- Is it possible that PIP silicone is associated with the increased incidence of local inflammatory reactions that have been reported with PIP implants compared with medical grade implants?

A thorough toxicological review has been conducted on the properties of the two most thoroughly studied siloxanes, D4 and D5. The conclusion is that these compounds are of low acute and chronic toxicity. They are not irritant and fail to cause skin sensitisation or immunotoxicity. They are not genotoxic, and chronic adverse effects occur only at high exposure levels in animal studies, and through mechanisms that are considered not relevant for human health. Thus, increased exposure to these compounds from a ruptured PIP implant will not represent an increased health risk compared with a conventional implant from another manufacturer. Although there are siloxanes other than D4 and D5 present in breast implants there is no evidence that their toxicological properties differ significantly from those of D4 and D5.

10.4. Consequences of implant failure

Implant failure does not necessarily result either immediately or longer term in identifiable adverse effects. There is no convincing evidence that the risk for adverse effects after rupture of PIP- implants is higher than the risk after rupture of devices from other manufacturers. The overall risk is higher for PIP-implants due to the higher risk for rupture

10.4.1. Adverse events and inflammatory reactions

Adverse effects due to free silicone and/or gel-bleed (in the form of siliconomas, lymphadenopathy, lumps etc.) have been reported less uniformly than implant ruptures.

Some cases of implant gel-bleed or rupture are associated with an inflammatory reaction locally or in the regional lymph nodes, and in some cases a pronounced reaction have been observed. In the UK report, the rate of explantation in patients with local clinical signs was 0.8% at five years rising to 2.1% at 10 years. In the French ANSM report the proportion of adverse effects with PIP implants was 16.6% per breast or in 18% of the studied women, including capsular contracture. If capsular contracture is subtracted, the figure was 8.8% per breast or 15.3% per woman.

10.4.2. Other effects

a) Capsular contraction. Capsular contracture is known to occur in all kind of breast implantation, and many factors can contribute to this. The risk of developing capsular contracture differs in clinical studies; in general from a few percent in augmentations to up to 30% in reconstructions over a period of 10 years. The reporting of adverse events, besides rupture, in PIP implantation is lower in most of the clinical studies.

b) Psychological effects. There is evidence that concerns about PIP implants have had a marked psychological impact on a considerable number of women.

c) Cancer. There is no evidence that PIP implants can cause breast cancer. Neither implant rupture nor local inflammation has been found to be associated with breast cancer or the rare anaplastic large cell lymphoma. There might be a somewhat increased risk of developing Anaplastic Large Cell Lymphoma (ALCL) in patients with breast implants. By now the number of known cases has increased to approximately 130 cases worldwide in women with breast implants. There is no indication of a specific association with PIP implants however.

There is one recent systematic review on breast implantation in general that concludes that cosmetic breast augmentation for aesthetic reasons may adversely affect the survival of women who are subsequently diagnosed as having breast cancer; presumably because of difficulties with diagnosing the cancer. These findings should be interpreted with caution as some studies included in the meta-analysis on survival did not adjust for potential cofounders. The increased risk of being diagnosed with a more advanced breast cancer among breast augmented women was found in women with a diversity of different breast implants which indicates that the potential adverse effect of the breast implants with regard to mammography is not implant specific.

10.5 Generic Risks and Benefit of removal of PIP silicone breast implants

In view of the high rupture rates, many women carrying breast implants can be expected within their lifetime to experience ruptured implants.

There is inevitably a higher intra and postoperative risk associated with the removal of ruptured implants than with intact implants. In case of implant rupture and/or in the presence of loco-regional inflammation or lymphadenopathy, explantation is advised.

The risk-benefit assessment of explantation should be made on a case by case basis and performed by an appropriately qualified and experienced plastic surgeon in collaboration with the woman. Factors to be included in the decision-making are: clinical symptoms, objective findings including ultrasonography or MRI, the integrity of the implant, the time since the implantation, and the psychological state of the patient.

In the case of PIP implants, early implant ruptures are predominant and 10-year implant survival is at the level of second generation implants from other manufacturers. The PIP implant contents have also been cited by a number of surgeons as having the consistency typical of second generation implants.

It is evident from the above that for an individual the risk from a specific implant cannot be entirely anticipated. Despite the uncertainties regarding the actual risk to individual patients and in view of the public concern, it may be considered advisable for women with PIP implants to be regularly informed about health risks and offered regular assessments. This could include: clinical examinations, individual counselling, and/or imaging with ultrasonography or MRI.

With regard to explantation of intact PIP implants as a precautionary approach, currently there are no convincing medical, toxicological or other data to justify this. However, based on individual assessment, explantation could be considered for women who experience psychological impairment due to carrying PIP implants, even in the absence of implant malfunction. Further consideration is that replacement of an implant cannot be carried out if the tissue around the explant is substantially inflamed

11. CONSIDERATION OF THE RESPONSES RECEIVED DURING THE CONSULTATION PROCESS

A public consultation on this opinion was open on the website of the EU non-food scientific committees from 29 October 2013 to 3 January 2014.

Information about the public consultation was broadly communicated to national authorities, international organisations and other stakeholders.

Six organisations and ten individuals participated in the public consultation providing specific comments and suggestions with the aim to improve the scientific basis of the opinion.

Each contribution was carefully considered by the SCENIHR and the scientific opinion has been reviewed to take into account relevant comments. The final opinion includes these changes; the literature has been updated with relevant publications.

All contributions received and the responses of the SCENIHR are available at:
http://ec.europa.eu/health/scientific_committees/consultations/public_consultations/scenihr_cons_14_en.htm

Some respondents appeared not to be aware that the purpose of the new opinion was to update the previous opinion in 2012 on the same topic. For this reason SCENIHR makes clear that:

- A comprehensive analysis of the literature relevant to this topic was not attempted. Only publications that were directly relevant for updating purposes were considered and the focus was on publications released in 2012 and 2013.
- Particular emphasis was given to data on rupture rates and studies by the competent Agencies of various countries. Information which could not be readily verified, although of interest, was not used in the opinion (in line with SCENIHR general policy[2]).
- Issues concerning risk management or legal aspects were not addressed because they are outside the remit of the SCENIHR mandate.

Respondents made comments on the following relevant issues.

i) Rupture rates

Several respondents provided additional information based on their experience regarding variation in rupture rates, requesting to include this information in the opinion. One respondent also expressed concerns that the basis for the risk assessment was primarily through a comparison of data on PIP implants against implants from other manufacturers.

The response of the SCENIHR is that information provided by respondents has confirmed the statement in the opinion that rupture rates in different clinics show considerable variation. The cause(s) of this variability in rupture rates may be due to the differences between batches of implants in the quality of the silicon and/or poor control of the manufacturing process. Other factors contributing to the variability in rupture rates are the differences of the way the incidence is identified and reported by different clinics. As a conclusion, SCENIHR considers that adding more information on the variability of rupture rates between clinics is unnecessary. Moreover, SCENHIR states that equivalence with devices of other manufacturers was the best available basis for analysing the data in consideration of the task set by the Commission.

[2] SCENIHR Memorandum on the use of the scientific literature for human health risk assessment purposes – weighing of evidence and expression of uncertainty- 19 March 2012

ii) Relationship between rupture and adverse effects

This issue was recognised by some respondents as critical. Some respondents referred to a series of references and medical claims related to the movement of silicone in the body (particularly in the armpits, neck and chest/lungs). Other respondents referred to some anecdotal information that around damaged PIP implants milky fluid is formed. A number of respondents underlined the importance of the release of polymeric silicones (gel) from ruptured implants in causing adverse effects such as local swelling and irritation and, finally, one contributor claimed that some of its work in the area of siloxane toxicity was inappropriately referenced.

The response of SCENIHR

- related to the contributions focused on the movement of silicon in the body: this issue is well covered in the opinion (see section 8.2).
- related to the list of references: the list of references was not taken into account because the most recent reference is from 2004 and therefore, the information is too dated to be considered again by the SCENIHR.
- related to the information that around damaged PIP implants there is milky fluid: this issue is not discussed in the opinion as the available evidence/information is anecdotal. This is interpreted as an indicator of a formation of a silicone emulsion rather than formation of a new substance.
- related to the release of polymeric silicones (gel): unfortunately there are no new data in regard to PIP devices nor on the migration of the gel for non-PIP devices and therefore it is not known whether this is an issue related to particular batches of PIP devices. There were reports that some PIP implants were produced without a barrier layer /membrane and this would lead to higher diffusion of silicone from the implant. (SCENIHR PIP Opinion, 2012, page 22). A statement concerning the lack of new data in regard to PIP devices and on the migration of the gel for non-PIP devices has been added to the opinion.
- The report on siloxane toxicity was fully considered in the preparation of the preliminary opinion and is now appropriately referenced.

iii) Psychological effects and their causes

The opinion notes that psychological effects may arise in patients who have, or have had PIP implants and it draws attention to the effects of the extensive and adverse publicity concerning PIP implants as an important contributor to these psychological effects. This view was challenged by one respondent.

The response of the SCENIHR is to acknowledge that for individual patients there may be other contributing factors, but the SCENIHR does not wish to change its view that adverse publicity is the major contributor for most patients suffering psychological effects. A note has been added to indicate that for individual patients there may be additional contributing factors.

Additions suggested by SCENIHR members
In reviewing the preliminary opinion it was noted that a mention of factors limiting explantation should be added, namely that replacement of an implant cannot be carried out if the tissue around the explant is substantially inflamed. This mention has now been included in the final opinion.

12. RECOMMENDATIONS FOR FURTHER WORK

The SCENIHR identified the need for the following actions.

12.1. Information to breast implant recipients

The SCENIHR stresses the importance that recipients of breast implants are informed of possible risks, including that of device failure, which increases with time. In view of the high rupture rates, the majority of women can be expected to experience a ruptured implant within their life span.

12.2. Improved reporting data on breast implants

It is the view of the SCENIHR that implementation of a registration system of breast implantations on a national or European level is of utmost importance for collecting and analysing data for research and risk assessment purposes. The questionnaire developed for this opinion could provide a valuable tool for this purpose. There is still a need for better reporting on breast implant failures, in particular on ruptures, through the mandatory vigilance reporting system to identify potential design problems earlier.

It would have been of tremendous help in developing the appropriate advice to patients and other stakeholders, including medical staff and health care planners, to be able to, with certainty, to identify PIP recipients. In the current situation, many women are unaware of the specifics of their breast implantation. Continuous surveillance of the different products on the market would enable development and improvements of safer and more compliant products as well as be a significant tool in the future scientific research and product monitoring.

12.3. Explant analysis

In order to identify why an implant has caused a significant adverse reaction, it is necessary to analyse the explant involved. Analysing every explant would be very complex, time consuming and expensive. Instead, a long term retrieval study should be implemented focusing on a representative sample of explanted devices. This would enable future studies on device failures, rupture mechanism, individual body-device interaction etc. This would also be of great assistance in the development of future safer devices and improving safety standards. The data, which have been analysed in this opinion, indicate that the properties of the shell are critical for implant safety. Further work is needed to identify how leakage of small molecules can be minimised and mechanical robustness ensured without compromising the performance of breast implants. This should include implementation of adequate redundant safety means such as a redundant shell and an improving the device-tissue boundary to minimize contraction risk.

An outline for such an implant retrieval study has been included in Appendix I.

12.4. Identifying the causes of irritant and other reactions

The findings of this opinion indicate that an irritant biological response (inflammation) following rupture of an implant can occur but that it is not due to the release of D4, D5 and/or D6.

A better understanding of the causes of the inflammatory and other reactions is needed. This should include how the surface of the shell impinges on the development and characteristics of the capsule.

12.5. Future clinical examinations

There is still a need for low cost reliable tests suitable for routine use to identify implant status (leakage, rupture) in patients. It is important to improve our understanding of inter-individual differences in vulnerability to the effects of a leaking/ruptured implant since the available data indicates there are substantial variations.

12.6. Qualification of surgeons

Although the SCENIHR has been unable to investigate the impact of poor surgery on implant failure it is concerned that implant operations may be carried out by individuals who are poorly qualified/ experienced to conduct breast implantations.

13. MINORITY OPINION

No minority opinion was expressed.

14. ABBREVIATIONS AND GLOSSARY OF TERMS

AFFSAPS then ANSM	Agence française de sécurité sanitaire des produits de santé Agence nationale de sécurité du mèdicament et des produits de santé
ALCL	Anaplastic Large Cell Lymphoma, very rare type of lymphoma
ANSM	Agence nationale de sécurité du medicament et des produits de santé) National Agency for the Safety of Medicines and Health Products
Baker grade I-IV	Clinical grading of capsular contracture. Grade I and II are no or slight detectable firmness due to fibrous capsule; grade III is significant firmness and stage IV with visible distortion and pain
Capsular contracture	Thickening of fibrous membrane/capsule around the implant resulting in distortion of the implant if serious (Baker grade III and IV)
D4	Octamethylcyclotetrasiloxane, low-molecular silicone
D5	Decamethylpentasiloxane, low-molecular silicone
D6	Dodecamethylcyclohexasiloxane, low-molecular silicone
Explantation	Operation with removal of the implant
FDA	Federal Drugs Agency (USA)
Fibrous capsule	Fibrous tissue, which is formed around an implant as a natural reaction to the foreign body
FTIR	Fourier Transform Infrared Spectroscopy
GC-MS	Gas Chromatography Mass Spectrometry
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
Implant first-generation	Implants from first production period with thick membrane and rather viscous/cohesive gel
Implant second-generation	Implants from 70'ties-80'ties with thinner shell and less viscous gel
Implant third-generation	Improved with a barrier layer in the membrane to minimize low-molecular migration. Can be textured or smooth. Gel more viscous/cohesive than second generation
Implant fourth-generation	Membrane as in third generation, gel even more cohesive. Can thus be manufactured with contoured shape

Inflammation	The biological response to an irritant with oedema, accumulation of white blood cells and immunological molecules accompanied by pain and swelling
IPRAS	International Confederation for Plastic Reconstructive and Aesthetic Surgery
LOAEL	The Lowest Observed (Adverse) Effect Level
LOEL	The Lowest Observed Effect Level
NOAEL	The No Observed (Adverse) Effect Level
Lymphadenopathies	Inflammation in lymph nodes
MHRA	Medicine and health care products regulatory agency UK
MoS	Margin of Safety
MPAS	Swedish Medical Products Agency
Periprosthetic fluid	Body fluid surrounding the implant in the implant pocket/within the fibrous capsule
PIP silicone gel filled breast implant	PIP implant
SCCS	EU Scientific Committee on Consumer Safety
SCENIHR	EU Scientific Committee on Emerging and Newly Identified Health Risks
Siliconoma	Free silicone in tissue with inflammatory reaction around the lump of silicone
TGA	Australian Therapeutic Goods Administration
Toxicokinetic	The absorption, distribution, metabolism and excretion of a chemical
Toxicodynamic	The adverse effects of a chemical

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16. ANNEXES

Appendix I

QUESTIONNAIRE ON BREAST IMPLANTS

In IPM the session time is limited to 90 minutes. This means that you should submit your reply within this time. If you exceed it, your reply will be lost. You might consider preparing your comments in a separate document and then importing them into this consultation response form.

This questionnaire should take approximately 7 minutes to complete.

NOTE: *The received individual contributions will be handled in such a way to protect medical confidentiality.*
Privacy statement

Importance of this questionnaire

The questionnaire is intended to cover only patients that undergo an explantation. The aim is to identify whether there are differences between patients that undergo an explantation of PIP breast implants compared with those from other manufacturers on:

i) The nature, frequency and/or severity of adverse effects prior to and at explantation and the correlation between these.
ii) The time to rupture and/or rupture frequency and /or nature and extent of rupture.
iii) The extent of correlation between i) and ii).

We need your help

The findings will be of great value in providing the evidence base for policy formulation, in increasing the safety of future breast implant devices, and in identifying patient symptoms that are most likely to be associated with implant failure. We recognise that to fill in this questionnaire will place demands on your time and we very much appreciate your willingness to participate in this important study. We will keep you informed of the findings both for your interest and to inform your practice.

We will be glad to acknowledge your contribution
The Scientific Committees of the European Commission follow the practice of acknowledging contributions to scientific opinions. Below, at the end of this questionnaire, please indicate if you would like to be acknowledged and have your name and/or professional affiliation added to the list of contributors to this study. The initial data collection phase will end on 31 March 2013. Please submit your data by this deadline. Thank you.

If you have any questions please contact:
Sanco-SCENIHR-Secretariat@ec.europa.eu

Questions marked with an asterisk * require an answer to be given.

1. Background information

1. Patient date of birth *
[Date]

2. Implantation data

2. Is there an implant on the RIGHT side? *
Yes No

2.1 Date of implantation *
[Date]

2.2 Please indicate the reason for implantation on the RIGHT side *

Aesthetic
Mastectomy due to malignant breast tumour
Other restorative

2.3 Please indicate the incision used for implantation on the RIGHT side. *
Periareolar
Inframammary
Axillary
Other

2.3.1 Please specify the other incision used. *

2.4 History of implantation: *
Without complications
With complications
Unknown

2.4.1 Please specify the complications. *

3. Post implantation data (RIGHT side)

3.1 Were regular checks carried out after the implantation? *
Yes
No
Unknown

3.2 Was there a history of physical trauma prior to the explant? *
Yes No

4. Implant data (RIGHT side)

If you do not have the information please indicate 'Not available'.

4.1 Name of the manufacturer of RIGHT implant. *

4.2 Serial or lot number of RIGHT implant. *

4.3 Size of RIGHT implant. *

4.4 Surface of RIGHT implant: *
Smooth
Textured

5. Explantation data and reason for explantation (RIGHT side)

5.1 Was the right implant explanted? *
Yes No

5.2 Date of explantation *
[Date]

5.3 Reason for explantation. Please select all relevant. *
Patient developed symptoms
Suspicion of rupture of the implant
Requested by the patient
Routine removal because of time elapsed since implantation
Implant displacement or aesthetic reasons

Other
National policy
Outcome of an assessment by the doctor

5.3.1 Please select the symptoms developed by the patient. *

Pain
Local swelling
Change in implant consistency and/or shape
Other
No symptoms

5.3.1.1 Please select the change in implant consistency. *

Softer breast
Harder breast

5.3.2 Please specify other reasons for explantation. *

6. Findings during explantation (RIGHT side)

6.1 RIGHT SIDE: local findings observed during explantation (please select all relevant) *

Free silicone within fibrous capsule
Milky fluid around the implant
Free silicone outside the fibrous capsule
Skin perforation
Suspicion of inflammation
Thickening or granulation of the capsule
Capsular calcification Granuloma within the breast glandular tissue
Implant rupture occured during the explantation
Suspicion of anaplastic large cell lymphoma
Suspicion of malignant breast tumours
Other

6.1.1 Please specify other local findings observed. *

6.2 Regional or systemic pathological findings observed during explantation (RIGHT side). Please select all

relevant: *

Inflammation
Infection
State of lymph nodes
Silicone beyond local area
Other malignant tumors
No findings

6.2.1 Please select for inflammation. *

Regional Systemic

6.2.2 Please select for infection. *

Regional
Systemic

6.2.3 Please select for state of lymph nodes. *

Enlarged axillary lymph nodes
Enlarged distant lymph nodes

6.2.4 Please select for silicone beyond local area. *

Silicone in axillary lymph nodes
Silicone in distant lymph nodes

6.2.5 Please select for other malignant tumors. *
Regional Systemic

7. State of explant after explantation (RIGHT side)

7.1.1 RIGHT implant visibly ruptured. *
Yes No

7.1.1.1 Please specify the rupture. *
Destroyed/melted
Pinhole Tear

7.1.2 RIGHT implant: change in implant consistency? *
Yes No

7.1.2.1 Please specify the change in implant consistency. *

7.1.3 RIGHT implant: Gel bleed? *
Yes No

7.1.3.1 Please specify (see pictures) Images courtesy of Professor Dr. Dirk W. Schubert, Centre for Silicone Breast Implant Investigation, Friedrich-Alexander Universität Erlangen-Nürnberg *
Cohesive
Less cohesive

7.1.4 RIGHT implant: Location of the failure: *
Anterior - central
Posterior - central
Peripheral - equatorial

7.1.4.1 Please estimate size of failure in mm for Anterior - central. *

7.1.4.2 Please estimate size of failure in mm for Posterior - central. *

7.1.4.3 Please estimate size of failure in mm for Peripheral - equatorial. *

7.2 RIGHT implant: additional information about the failure:
7.3 Were laboratory investigations (e.g. anatomopathology, microbiology, etc.) performed for this patient? *
Yes No

7.3.1 Please provide a summary.
7.4 Were laboratory tests (e.g. mechanical, toxicology, chemical testing) performed on the implant? *
Yes No

7.4.1 Please provide a summary.

8. Implantation data (LEFT side)

8. Is there an implant on the LEFT side? *
Yes No

8.1 Date of implantation *

[Date]

8.2 Please indicate the reason for implantation on the LEFT side. *
Aesthetic
Mastectomy due to malignant breast tumour
Other restorative

8.3 Please indicate the incision used for implantation on the LEFT side. *
Periareolar
Inframammary
Axillary
Other

8.3.1 Please specify the other incision used. *

8.4 History of implantation: *
Without complications
With complications

8.4.1 Please specify the complications. *

9. Post implantation data (LEFT side)

9.1 Were regular checks carried out after the implantation? *
Yes
No
Unknown

9.2 Was there a history of physical trauma prior to the explant? *
Yes No

10. Implant data (LEFT side)

If you do not have the information please indicate 'Not available'.

10.1 Name of the manufacturer of LEFT implant. *

10.2 Serial or lot number of LEFT implant. *

10.3 Size of LEFT implant. *

10.4 Surface of the LEFT implant: *
Smooth
Textured

11. Explantation data and reason for explantation (LEFT side)

11.1 Was the left implant explanted? *
Yes No

11.2 Date of explantation *
[Date]

11.3 Reason for explantation. Please select all relevant. *
Patient developed symptoms
Routine removal because of time elapsed since implantation
National policy

Suspicion of rupture of the implant
Implant displacement or aesthetic reasons
Outcome of an assessment by the doctor
Requested by patient
Other

11.3.1 Please select the symptoms developed by the patient. *
Pain
Local swelling
Change in implant consistency and/or shape
Other

11.3.1.1 Please select the change in implant consistency. *
Softer breast
Harder breast

11.3.2 Please specify other reasons for explantation. *

12. Findings during explantation (LEFT side)

12.1 LEFT SIDE: local findings observed during explantation (please select all relevant) *
Free silicone within fibrous capsule
Milky fluid around the implant
Free silicone outside the fibrous capsule
Skin perforation
Suspicion of inflammation
Thickening or granulation of the capsule
Capsular calcification
Granuloma within the breast glandular tissue
Implant rupture occurred during the explantation
Suspicion of anaplastic large cell lymphoma
Suspicion of malignant breast tumours
Other

12.1.1 Please specify other local findings observed. *
12.2 Regional or systemic pathological findings observed during explantation (LEFT side). Please select all relevant: *
Inflammation
Infection
State of lymph nodes
Silicone beyond local area
Other malignant tumours
No findings

12.2.1 Please select for inflammation. *
Regional
Systemic

12.2.2 Please select for infection. *
Regional
Systemic

12.2.3 Please select for state of lymph nodes. *
Enlarged axillary lymph nodes
Enlarged distant lymph nodes

12.2.4 Please select for silicone beyond local area. *
Regional

Systemic

12.2.5 Please select for malignant tumours. *
Regional
Systemic

13. State of explant (LEFT side)

13.1.1 LEFT implant visibly ruptured. *
Yes No

13.1.1.1 Please specify the rupture. *
Destroyed/melted
Pinhole
Tear

13.1.2 LEFT implant: change in implant consistency? *
Yes No

13.1.2.1 Please specify change in implant consistency. *

13.1.3 LEFT implant: Gel bleed? *
Yes No

13.1.3.1 Please specify. (see pictures) Images courtesy of Professor Dr. Dirk W. Schubert, Centre for Silicone Breast Implant Investigation, Friedrich-Alexander Universität Erlangen-Nürnberg *
Cohesive
Less cohesive

13.1.4 LEFT implant: Location of the failure: *
Peripheral - equatorial
Anterior - central
Posterior - central

13.1.4.1 Please estimate size of failure in mm for Peripheral - equatorial. *

13.1.4.2 Please estimate size of failure in mm for Anterior - central. *

13.1.4.3 Please estimate size of failure in mm for Posterior - central. *

13.2 LEFT implant: additional information about the failure:

13.3 Were laboratory investigations (e.g. anatomopathology, microbiology, etc.) performed for this patient? *
Yes No

13.3.1 Please provide a summary.
13.4 Were laboratory tests (e.g. mechanical, toxicology, chemical testing) performed on the implant? *
Yes No

13.4.1 Please provide a summary.

14. Information on the respondent

14.1 Name of respondent *

14.2 Job position *

14.3 Contact details respondent (e-mail and/or phone number). *

14.4 Clinic/hospital address. *

15. Additional comments

15.1 Additional comments (If your comments are relevant to a specific topic listed above, please indicate the number of the question.)

15.2 The Scientific Committees of the European Commission follow the practice of acknowledging contributions to scientific opinions. Do you wish to be acknowledged? *
Yes No

15.3 How would you like to be acknowledged? By name, name and professional affiliation, professional affiliation, etc. *

Outline for explant analysis

Selection of explants to be analysed

Explants should meet one or more of the following criteria:

- Left and right implants inserted at the same time. At explantation, reaction around one breast but not the other (both explants need to be analysed).
- Patient has a severe local reaction in both breasts.
- Patient has a severe systemic reaction.
- Left and right implants inserted at the same time. At explantation, rupture of one explant but the other appears to be normal.

To establish a coordinated, reliable and funded scheme between member states for explant collection, storage and subsequently analysis and processing of the data, which can be directly linked to the questionnaire responses.

To utilise the responses from the questionnaires a substantial data processing is necessary. This is substantially greater than a normal (unpaid) task assignment for a member of a working group. Funding support will therefore be needed for an individual/organisation to carry out this work.

Without such support it is unlikely that we will reach an understanding of:

-the causes of implant failure

-the relationship between implant damage and adverse effects in the patient

-the components of concern in the implants

-the parameters to be used for future bio-monitoring.

Proposed procedure.

i) Sample storage.
- Store all explants in plastic containers at room temperature. Controls may be left in original containers. All containers should be labelled.
- Visually and physically inspect all explants and document explant status.
- Develop a detailed explant/control data file.
- Select explants and controls for testing and analysis based on information in data file.

ii) Preparation method
  - Detailed visual and physical inspection of failure regions.
  - Documentation of failure regions and types of failure regions.
  - Documentation of weigh of explants and controls and verification of filler volumes.
  - Cleaning of shells
  - Measuring of shell thicknesses around entire shell.
- Comparison of weight and thickness with original specifications provided by manufacturers.
    - Microscopically analysis of shells and failure regions.
    - Field emission scanning electron microscopy.
    - Optical microscopy?

iii) Mechanical analysis
  - Preparation of tensile specimens – approximately five dog bone specimens using die C ½ scale or die H2.

- Measure force-to-break and tensile stress using an Instron or comparable testing apparatus.
- Simultaneously measure elongation using a video or mechanical extensometer.
- Measure 100%, 200%, 300%, 400%, and 500% moduli.
- Record stress-strain curve.
- If patch failures are significant, prepare patch specimens and evaluate patch strength.
- Compare explant and control data.
- Compare PIP data with European and US standards, and also with Allergan, J&J, and Dow Corning data.
- Applying a benchmarking of implant shell quality utilizing the procedure and data representation according to Schubert et al 2013.

iv) Chemical analysis
- Shell and gel extraction.
- Analysis of metal components.
- Low and high molecular weight analysis.

Appendix II

Summary of case reports with adverse effects after PIP implantation

Lahiri and Waters in 2006 were the first to report a case of a ruptured PIP implant. The patient had breast augmentation with PIP implants 6 years before. Already two years after implantation she presented with multiple enlarged lymph nodes in the right axilla. No sign of implant rupture or breast disease could be found at that time. However, 18 months later ultrasound showed possible leakage of the right implant and fine needle aspiration of the lymph nodes showed silicone granuloma. She was operated and the implant was found ruptured with a large tear on the backside. Eight lymph nodes in the axilla were removed and revealed silicone lymphadenitis and histology examination of the fibrous capsule showed silicone granuloma.

Berry, in 2007, in response to the above, reported a case of PIP implant rupture only 3 years after implantation. The patient presented with an enlarged right axillary lymph node and enlarged right breast. The lymph node was removed and found to contain vacuolated cells, foamy macrophages and multinucleated giant cells (silicone and foreign body reaction). The implant was widely torn and surrounded by cloudy viscous fluid. The author questioned the reliability of PIP implants and informed that he intended to discontinue the use of PIP implants.

Cawrse and Pickford (2011) reported a case of a patient who 5 years after bilateral PIP breast implant augmentation presented with a 4-week period of swelling of the left breast with tender and marked axillary lymphadenopathy. A puncture from the breast revealed sterile yellowish turbid fluid, which recurred within hours and the patient developed reddish papules on the left antecubital fossa, on the left hand, on the left thigh, and on the right hand. The patient was operated. The fibrous capsule in both breasts was found grossly thickened and bilaterally floridly inflamed. On the left side, yellowish fluid was abundant. Both implants seemed intact, but with surface stickiness suggestive of rupture. No bacteria were found at microbiology examination. Histological analysis of the fibrous capsule revealed florid non-caseating granulomatous inflammation surrounding clear spaces consistent with silicone particles. Biopsy of a papule in the left cubital area revealed the same granulomatous inflammation, but no silicone. Three months after partial capsulectomy and change of implants the breasts remained asymptomatic and the skin papules had flattened and showed reduced erythema. The authors consider the skin lesions proof of migrating silicone granulomata.

Manikavasagar et al. (2013) found a heavy spread of lymph nodes containing silicone in a patient presenting with bilateral supraclavicular fullness. Several enlarged lymph nodes were found in the region. The patient had PIP breast implants 11 years previously for a prepectoral breast augmentation. She underwent surgical removal of the ruptured breast implants as well as excision of siliconomas and axillary lymph nodes up to level III. Lymph nodes ranged in size from 5- 45 mm in maximum dimension. Histological examination confirmed reactive lymphadenopathy presumed secondary to silicone exposition

Kolios (2013) describes widespread lymphadenopathy in both the right axilla and right neck region in a 29-year-old woman who received PIP implants 5 years earlier for breast augmentation. The right implant was found ruptured and 14 enlarged lymph nodes from the axilla to level II were resected. Histological examination of the lymph nodes revealed massive lymphadenopathy.

Dieterich et al. (2013) described a case of a unilateral ruptured PIP implant in an asymptomatic 29-year old woman with cosmetic breast implant. The augmentation was

performed in 2004 in another center and ultrasonography found that the left implant was ruptured. At surgery, the gel was non-cohesive, flaking, yellowish, liquid gel easily removed. Capsulectomy was performed at both sides and samples from suspicious and unsuspicious areas were sent for histology. Normal fibrotic tissue was found at the site of the intact implant, while at the site corresponding to the implant rupture, extensive silicone invasion into the tissue, extended fibrosis with macrophages, and silicone granulomas with vacuolated histiocytes was observed, but no sign of malignancy. The authors recommend routine histological examination in cases of removal of PIP implants, but do not find reason to test for anaplastic large cell lymphoma on a routine basis.

Gubitosi (2012) describe a case of a 47-year old woman who in 1998 received PIP implants for breast augmentation. She presented with a 2.5 cm. nodule in the breast adjacent to the breast implant capsule. Histology revealed infiltrating ductal carcinoma. The patient underwent skin-sparing mastectomy and immediate reconstruction with a submuscular implant. Histological examination revealed granulomatous inflammation by giant cells around extraneous material. Lymph nodes, negative of cancer, showed extensive accumulation of foamy macrophages containing extraneous material. The authors suggest that chronic inflammation could increase risk of breast cancer, and advocate exchange of old implants. It should be noted that no causal association between breast cancer and silicone granuloma/ foreign body reaction could be made based on one such case. With the current high number of breast cancers and high number of silicone breast implant recipients, a case of having both - a complicated rupture and breast cancer - must be expected once in a while.

Garcia Callejo (2013) in a paper written in Spanish, but with an English abstract, described neck lymphadenitis due to silicone granuloma in the presence of mammary implants. Within a 10-year period, the authors identified 12 cases with lymphadenopathies, in the neck containing silicone particles, histologically confirmed by fine needle aspiration. All the women had PIP implants (personal communication). They represented 3.5% of patients attended for neck lymph node study. They removed those detected by physical examination and CT in 5 cases, due to pathological characteristics of the node or a previous malignant history. In 2 of these nodes recurred, and node size also increased in 2 of the other 7 non-operated cases. After implant removal, silicone leakage was observed in only 7 cases. The authors concluded that cohesive gel silicone used for mammary implants can generate increased neck lymphadenopathies as a secondary effect due to systemic reactions against the silicone when it migrates in cases of implant failure. Excisions of those nodes usually does not offer good long-term results.

Malata et al. (2013 in a recent letter informed about 6 consecutive operations on women with PIP implants, originally operated elsewhere by non-plastic surgeons. The women all had clinical symptoms of implant rupture, with at least two of the following five features: breast discomfort, axillary discomfort, breast swelling, axillary swelling, or change in breast consistency. All women underwent sonography and MRI. All patients had at least one ruptured implant. Findings during surgery included silicone extravasation with purulent material in the pockets. Half of the patients had soft tissue silicone granuloma and underwent axillary excisions. The authors recommend a clinical algorithm, which includes total capsulectomy for all PIP, implanted women.

Breast implant generations – definition:

For simplicity and to compare implants over studies, implants have been categorized into generations.

Ideally, the grouping should be taking design specifics into consideration: shell resilience, thickness, permeability and surface among other things. The gel-composition should be known; amount of cross-linked silicone, amount of low-molecular siloxanes, viscosity etc. These parameters are rarely publicly known, and instead some common features have been used to categorize implants into generations.

There seems to be consensus in most of the literature that the first-generation implants had thick shells and the gel was rather viscous. The very early implants also had a Dacron patch to secure stable positioning. Due to the firmness of the implants, softer pliable second-generation implants with thinner shells and less viscous gel were produced. (All smooth surfaces). Due to high rupture rates, high rate of gel-bleed, and also high rate of capsular contracture, implants with barrier-coated low-bleed shells were marketed and later classified as third-generation implants. These implants are still produced and with both smooth and textured surfaces. Most agree that the fourth generation implants have a higher cohesiveness/cross-linking of the silicone gel, which allows for production of contoured implants. Some consider a fifth generation to be implants with a two-component form stable gel. The membranes used in the later generation implants seem to be the same as in the third generation implants from the different companies.

The manufactures do not comply with this categorization; each have their own terminology of describing the product specifics for the own implants.

For simplicity, categorization according to calendar year of production/implantation or a hybrid between this and implant specifics is commonly used. But is should be noted, that some manufactures have produced more than one generation of implants at the same time, and implants can be used for up to 5 years after production. One firm may have improved technology in one period, others before or later. In addition, there are quite large discrepancies as to when the different models have been available in the different countries. Up until 1992, the newer models of silicone breast implants were generally marketed in the US first, followed by Canada and some of the larger European countries. After 1992, where free use of silicone breast implants were restricted in the US the marketing of new products have been focused on the European, South American and Asian market.

Appendix III

Published studies of silicone breast implant rupture

	Genera-tions*	Number of women	implants	Median implant age (range), years	% Ruptured by	women implant	Method of examination
PIP studies Implants from 2001-2010	All PIP are 3rd or 4th						
UK expert group study – explanted devices only 2012			1,565	?		31.1 (incl. gel-bleed)	Surgery
French ASNM study 2013		16,426	28,276	? 5-6 for ruptured		15.6	Surgery
Spanish study 2013		1500	2755	?	25.6		Surgery
Spanish Survival estimate 2013				5 year 10 year	10 45		
Australian TGA Study** 2012		~ 5000	13.000	?		Overall, 3.3	Surgery or imaging
Swedish MPA study** 2013		4,082			2.2		Surgery
Berry and Stanek, 2013 survival estimate		460		10		19-40	Sonography and surgery

Maijers and Niessen, 2012***		112	224	9.3 (9.2 - 11.1)	33	24.1	MRI
Quba and Quba		338	676	7.8 (1-13)	35.2	21.3	Surgery
Chummun and McLean, 2013		39	78	7		21.8	Surgery
Crouzet et al, 2012		71	76	1.8		3.9	Surgery
Aktuof et al., 2012		99	192	? implanted in 2005-10	17.2	12	Sonography and MRI
Carillon et al, 2012		31	33	1.3		9	MRI of all Surgery of 8

	Generations*	Number of women, implants		Median implant age (range), years	% Ruptured by women implant		Method of examination
Non-PIP studies							
Brown et al. 2000 Different implants, 70% Surgitek****	largely 2nd		687	16.4 (6.4-28)	69	55	MRI
Hölmich et al. 2001. Different implants	1 st, 2nd, 3rd		533	12 (2-25)	36	26	MRI
Subset of above study*****	3rd		263	7 (3-11)		7-14	MRI
Hölmich et al. 2003. Different implants. Survival estimate	3rd			10		15-17	MRI
Collis and Sharpe, 2007 Mentor implants	3rd	149	298	8.9 (4.8-13.5)	15	11	MRI
Mentor FDA 6-year follow-up Study Cunningham et al. 2009 ****	3th	420 (50% i n last MRI)		6	Overall 3.7 (1.1-11.6) ****	2.6	MRI and Kaplan Meier estimate
Inamed/Allergan FDA 6- year follow-up Study Spear et al, 2007****	3th	30 % of 715		6	(2.3-9.3) ****	3.5	MRI and Kaplan Meier estimate
Inamed/Allergan FDA 10- year follow-up, FDA 2011******	3th			10	(6.3-27.2) ****		MRI and Kaplan Meier estimate
Mentor FDA 8-year follow-up, FDA 2011******	3th			8	(13.6-21.3) ****		MRI and Kaplan Meier estimate

Heden et al.2006 Inamed/Allergan	3rd	106	199	10.9 (9.5-13.2)		8	MRI
Heden et al. 2009 Allergan 410	4th	163	300	8 (5-11)		1.7	MRI
Allergan/Natrelle FDA 6- year follow-up study, Maxwell et al. 2012 ****	4th	30% of 941		6	6.4	3.8	MRI and Kaplan Meier estimate
Sientra/Silimed FDA 5- year follow-up study Stevens et al. 2012 ****	4th	571		5	Overall 1.8 (0-4.2) ****		MRI and Kaplan Meier estimate
Mentor CPG FDA 6-year follow-up study Hammond et al, 2012 ****	4th	419		6	(0-2.9) ****		MRI and Kaplan Meier estimate

* Generations is a simplified categorization based best on implant design and if not known then on calendar time of production. See appendix for explanation

** Australian and Swedish figures are based on reports to TGA/MPA, including confirmed ruptures. Figures are presumably underreported.

*** This study included PIP implants from 2000 and 2001 and found no difference in ruptures.

**** Surgitek implants were not produced after 1991 and have been found with higher rupture rates than other comparable implants.

**** 4 cohorts of women participate in the FDA follow-up studies: augmentation, augmentation revision, reconstruction and reconstruction revision, number of ruptures differ among cohorts

***** Numbers differ depending on definition of generation used.

****** These reports do not present overall rupture rates or by implant rupture rates. The vast majority of implants in both groups are primary augmentation which have the lowest rate of rupture. Follow-up was 66% for women with Allergan implants and 58% for women with Mentor implants.