Agence nationale de sécurité du médicament et des produits de santé

Report

PIP Breast Implants

Situation update

April 2013

ansm.sante.fr

Executive Summary: Situation Update on PIP Breast Implants

An Afssaps inspection was conducted on the premises of the company PIP from 16 to 18 March 2010 after it had been alerted by a surgeon and because of the increase in medical device incident reports and fruitless discussions with the company who were unable to explain these problems. Major deviations with respect to regulations and safety were noted and subsequently transmitted to the Public Prosecutor and the Director General of the Agence Française de Sécurité Sanitaire des Produits de Santé (Afssaps - French Health Products Safety Agency) who took the health policy decision on 29 March 2010, to suspend the marketing, distribution, export and use of silicone breast implants manufactured by this company. This decision was brought to the attention of the European authorities and other countries in which the implants were distributed.

Since 30 March 2010, follow-up recommendations for health professionals and information for patients fitted with these implants have been distributed and are regularly updated by Afssaps. In November 2011, the French Minister of Labour, Employment and Health and the Secretary of State for Health announced that they wanted the explantation of PIP implants to be offered to women during an interview with their surgeon, even if there were no clinical signs of implant failure.

On 1 February 2012, Afssaps, jointly with the General Directorate of Health (DGS) and on request of the Minister for Health, published a report on the series of controls carried out by the health authorities on the company PIP[1]. The Agency has since periodically transmitted a summary of adverse effect reports related to PIP silicone breast implants.

A one-year assessment of the reports is presented in this situation update. This report also includes data about the safety evaluation of PIP silicone gel implants performed in France and abroad.

On the basis of data available to ANSM including sales volumes, the Agency has estimated that at the time of the marketing ban of 30 March 2010, 30,000 women had been fitted with PIP silicone breast implants.

The data collected by the ANSM up to December 2012, show that 14,990 women had their PIP silicone gel implants explanted between 2001 and December 2012. Taking into account the known under-reporting of medical device incidents, the number of women actually explanted may be greater than the number of cases reported to the Agency.

A total of 5,048 women encountered at least one implant failure and 2,697 at least one adverse event. These figures may not add up as the same woman may experience both implant failure and adverse effects.

These explantations were performed after the detection of implant failure or a clinical sign. They can also be performed as a precautionary measure.

- **Explantations performed after detection of an adverse event**

At the end of December 2012, 4,061 women had undergone explantation after the detection of an adverse event.
These events can be classed in two groups: implant failure or an adverse effect observed in the patient. Both types of event may occur in the same woman.
2,703 women reported a rupture with clinical signs or detection during an ultrasound scan to ANSM corresponding to a total of 3,263 ruptured implants. Ruptures occurred during the first years after

[1] Update on checking procedures performed by the health authorities on the Poly Implant Prothèse Company, DGS/Afssaps
http://ansm.sante.fr/content/download/44078/572467/version/2/file/Rapport_complet+anglais+PIP_DEF.pdf

implantation and earlier (average 6.3 years) with PIP implants in comparison with the usual longevity of breast implants which is more than 10 years.
A total of 1,726 explanted women had at least one adverse effect, corresponding to 2,276 implants. These reactions were observed with or without an implant failure report and mainly involved inflammatory reactions. They occurred during the first years after implantation (mean time of 6.1 years).

- **Preventive explantations**

Since the health policy decision of March 2010 and until end December 2012, 10,900 women underwent preventive explantation (explantation after the patient asked to have the PIP implant removed, with no previous clinical or ultrasound sign of an adverse event).
8,641 (79%) had no failure of their implant(s), or adverse effects.
2,259 (21%) women presented an adverse event. These adverse events corresponded to implant failure (rupture, gel-bleed etc.) in 1,603 women and/or an adverse effect not detected by the tests performed before explantation in 971 women (capsule, effusions etc.).

- **Tumours in women with PIP implants**

A total of 64 cases of breast cancer had been reported to the Agency at the end of December 2012 in women with PIP silicone gel implants.
No new cases of anaplastic large cell lymphoma have been reported in women with PIP silicone gel implants since November 2011.
According to the opinion of the Institut National du Cancer (INCA - French National Cancer Institute) and experts from the European Commission, the reported tumours are not related to the characteristics of PIP implants.

Contents

Capsule or Capsular Contracture

Fibrous capsule formation around the breast implant. The capsule is a type of membrane that forms around a foreign material in order to isolate it and protect the body. It is a normal reaction to a foreign body. However, the membrane sometimes thickens and forms a genuine fibrous capsule and is then called a capsular contracture. The formation of this contracture is often accompanied by discomfort, pain and excessive firmness of the breasts. The frequency of this complication cannot be accurately estimated as it varies according to the type, volume and quality of the implant but also on the implantation conditions. Capsular contractures can have many origins.

Cytotoxicity

Property of a chemical or biological agent enabling it to alter or destroy cells

Medical device (MD)

Any instrument, apparatus, equipment, material, product, except for products of human origin, or other article used alone or in combination, including accessories and software intended by its manufacturer to be used specifically for medical purposes and whose principal intended action is not achieved by pharmacological, immunological or metabolic means, but whose function may be assisted by such means. The software intended by its manufacturer to be used specifically for diagnostic or therapeutic purposes is also a medical device.

Health policy decision (**DPS)**:

If the marketing or use of a health product gives rise to a risk for public health, ANSM can take health policy decisions under the conditions specified in the Code of Public Health.

These policy decisions may concern:

- Products or activities subject to authorisation or registration. In this case, the control measures (suspension, revocation, restriction) are provided for by the laws and regulations governing each product or activity.
- Products or activities not subject to authorisation or registration (MD, cosmetics for example). In this case, the control measures are laid down by Articles L.5312-1 et seq. of the Code of Public Health.

These policy decisions are strong legal acts and result from a scientific assessment and regulatory process ensuring the proportionality of the measure to the health risk. An adversarial procedure with the operator concerned by the decision takes place before signing the health policy decision, except in the case of a public health emergency. A health policy decision can be opposed by the interested party on notification and by third parties after publication, in particular in the *Journal Officiel*. A health policy decision may be reversed by a new decision, i.e. the previously issued authorisation may be restituted or a temporary or permanent ban lifted as soon as the findings motivating the policy decisions have been refuted.

DGS

Directorate General of Health

Genotoxicity

A genotoxic substance has a harmful effect on the structure of the genome.

Device vigilance

Monitoring of incidents or potential incidents, resulting from the use of medical devices after their marketing.

CE mark

CE (Conformité Européenne) mark that signifies a product meets the accepted standards of the applicable directives and that the products have been submitted to the conformity evaluation procedure in accordance with guidelines. The CE mark is affixed before marketing.

The three stakeholders of CE marking:

- Manufacturer: responsible for marketing, chooses the notified body and affixes the CE mark once it is obtained.
- Notified Body: assesses the compliance of the procedure followed by the manufacturer to demonstrate compliance with the essential requirements and issues the CE certificate.
- Competent authority:
  - Appoints and inspects notified bodies
  - Monitors the market
  - Centralises and evaluates surveillance data
  - Takes the appropriate health policy measures

Devices that are not custom-made or intended for clinical trials which are marketed or used in France must bear the CE mark.

MHRA

Medicines and Healthcare products Regulatory Agency: competent authority in the UK for health product safety

NuSil

Gel specially formulated for the manufacture of breast implants. This gel was declared in the CE marking dossier technical file for PIP implants. It consists of two components (A) and (B) that the implant manufacturer must mix in defined proportions of 3A/1B using a protocol drawn up by the supplier NUSIL. Each of these components contains reactive elements, and in particular a platinum-based catalyst, which initiate the polymerisation reaction when they come in contact. They also contain a non-reactive oil that remains "trapped" in the cross-linked network, thereby forming a gel.

Gel-bleed (gel-sweat)

The phenomenon of gel-bleed (or gel-sweat) is a mechanical complication involving the leaking of the silicone through the shell of an intact implant. It is a silent phenomenon and not detectable by imaging. Moreover, after an implant rupture, this phenomenon is masked by the presence of silicone in the implant pocket. Hence, gel-bleed is usually only detected after preventive explantation of intact implants.

Inflammatory reactions

Stereotyped reaction of the immune defence system, to injury.
The following are considered to be inflammatory reactions:

- Capsules,
- Inflammation or infection,
- Effusions,
- Lymphorrhoea,
- Siliconoma,
- Lymph node enlargement,
- Necrosis,
- Induration,
- Nodules,

Implant rupture

According to medical literature, the term "deflation" of the implant is associated with breast implants filled with saline and the term rupture concerns implants containing silicone gel. However, according to the experts, the rupture of the shell causes the deflation of the implant whatever the filling product. The terms "deflation and rupture" are therefore grouped together in the same class. Several factors cause the deflation or rupture of the implant, including:

- texturing of the implant surface which increases its rigidity and can weaken the shell,
- insufficient or excessive filling of the implant above or below the implant characteristics weakening its mechanical properties,
- damage, however minor to the shell caused by surgical instruments
- performing strenuous physical activity which is not indicated in women with breast implants
- during a mammography examination around the areola, excessive pressure on the breast can cause the opening of the valve and cause an effusion of the filling fluid.
- a defect of the weld
- violent trauma (car accident, for example)
- age of the implant which is the major cause of implant failure. The more the implant is exposed to heavy wear and regular damage the more its shell is likely to break. The probability of breast implant failure therefore increases with time after implantation. Consequently, breast implants should not be considered to be lifetime devices.

Capsular contracture or fibrous calcification may abrade the shell of the prosthesis and cause it to break.

SCENIHR

Scientific Committee on Emerging and Newly Identified Health Risks: Scientific Committee of the European Commission

TGA

Therapeutic Goods Administration: competent Australian authority for health product safety

Sweating

See gel-bleed

Introduction

Breast augmentation surgery has existed since the 1900s. The techniques used have gradually improved and really encouraging results were first obtained at the end of World War II. Several types of implant have been tested over the generations. The most commonly used solution today is still the implant with a silicone membrane filled with a cohesive silicone gel. This preference is confirmed each year by the increasing sales of silicone gel implants. The advantage of this type of implant over saline-filled implants is that it more closely resembles the natural shape and density of the breast.
This mammoplasty is performed either for breast reconstruction after mastectomy or for cosmetic purposes.

The company PIP has marketed implants containing silicone gels since 2001.

An Afssaps inspection was conducted on the premises of the company PIP from 16 to 18 March 2010 after it had been alerted by a surgeon and because of the increase in medical device incident reports and fruitless discussions with the company who were unable to explain these problems. Major deviations with respect to regulations and safety were noted and subsequently transmitted to the Director General of the Agence Française de Sécurité Sanitaire des Produits de Santé (Afssaps - French Health Products Safety Agency) who took the health policy decision on 29 March 2010, to suspend the marketing, distribution, export and use of silicone breast implants manufactured by this company.

Since March 30, 2010, follow-up recommendations for the attention of health professionals and information for the attention of patients with these implants have been distributed and are regularly updated by the Afssaps.

In November 2011, the death of a patient with PIP brand implants from anaplastic large cell lymphoma was reported to AFSSAPS. This event had a strong impact on the public and drew the attention of health professionals and women to PIP breast implants leading to numerous and often retrospective medical device incident reports.

The Minister of Labour, Employment and Health requested on 7 December 2011 to the Director General of Health and the Director General of AFSSAPS a status report on all the controls carried out by health authorities on the company PIP.

The Directorate General of Health (DGS) asked the National Cancer Institute (INCA) to issue an opinion on the possible risks of anaplastic lymphoma of the breast and breast adenocarcinoma in women with PIP implants. In its opinion of 22 December 2011, INCa concluded that there was no excess risk of anaplastic large cell lymphoma in women with PIP breast implants compared to other brands, nor any increased risk of breast adenocarcinoma either in relation to other breast implants or the general population.

After reading the INCa report, in November 2011, the Minister of Labour, Employment and Health and the Secretary of State for Health announced that they wanted explantation of PIP implants to be proposed to women during an interview with their surgeon, even if they presented no clinical signs of deterioration of the implant.

On 1 February 2012, Afssaps jointly with the DGS and on the request of the Minister for Health published a situation update on the series of controls carried out by the health authorities on the

company PIP[1]. The Agency has since periodically transmitted a summary of adverse effect reports related to PIP breast implants pre-filled with silicone gel.

This new assessment was made one year after the latest recommendations for women with PIP implants and 3 years after market withdrawal of PIP implants.

It was drafted in order to share the available information about the current state of knowledge on the subject in particular with women with implants and health professionals.

The first part of this report is devoted to device vigilance data on implant malfunctions and the effects seen in women, reported since the health policy decision of the Agency on 30 March 2010.

The second part reviews the safety assessment data on PIP silicone gel implants obtained in France.

Finally, the third part presents the data available in other countries and compares them to the French data.

The conclusion of this report outlines the future secondary action plan.

[1] Update on checking procedures performed by the health authorities on the Poly Implant Prothèse Company, DGS/Afssaps http://ansm.sante.fr/content/download/44078/572467/version/2/file/Rapport_complet+anglais+PIP_DEF.pdf

1. Medical Device Vigilance Data: implant failures and adverse events observed in French women with PIP implants

1.1 Population of women with PIP silicone gel implants

Women may receive breast implants for two reasons:

- Aesthetic choice
- A situation requiring reconstruction surgery usually after cancer, reconstruction for congenital malformations remains rare.

> Women fitted with breast implants for cosmetic purposes

According to the report of the European Scientific Committee SCENIHR on the safety of PIP silicone gel breast implants, women who receive breast implants for cosmetic reasons are usually healthy with normal weight to slim and have given birth. These women smoke more than the average population.[2]

The average age of implantation is 32 years (15-60 years).

> Women with breast implants for reconstruction surgery

Reconstruction surgery for cancer is performed for two reasons:

- secondary reconstruction following treatment,
- primary reconstruction during mastectomy (including cases of prophylactic mastectomy)

The average age of implantation is 50 years (21-72 years).[2]

The SCENIHR report also points out that complications after breast implants are more severe in the cohort of women who underwent reconstruction than among patients who had breast augmentation for cosmetic purposes.[3]

The report also shows that complications are multifactorial and may, for example, be due to the surgical technique, the amount of tissue available, the laxity of the breast tissue, surgical trauma concomitant with the mastectomy in primary cases and to the initial tissue lesions after chemotherapy and radiotherapy in secondary cases.

[2] The safety of Poly Implant Prothèse (PIP) Silicone Breast Implants, SCENIHR, version of 1st February 2012
[3] Henriksen et al., 2005, Cunningham and McCue 2009, Spear et al., 200

> Number of women fitted in France with PIP silicone gel implants

The data available to ANSM indicate that 69,383 silicone gel implants manufactured by Poly Implant Prothèse were distributed in France between 2001 and 30 March 2010, when the ANSM suspended their marketing (Table 1).

Year	Number of prostheses sold
2001	4572
2002	8339
2003	9744
2004	8996
2005	7460
2006	7929
2007	8042
2008	7251
2009	5640
2010	1410
TOTAL	69383

Table 1. Estimated sales volume

It is estimated that 80% of breast implants are implanted for cosmetic purposes and about 20% for breast reconstruction[2] .

Using these sales volumes, the agency estimated that the number of women with PIP silicone breast implants in France was about 30,000 at the time of the ban on marketing on 30 March 2010, using the following calculation (Figure 1):

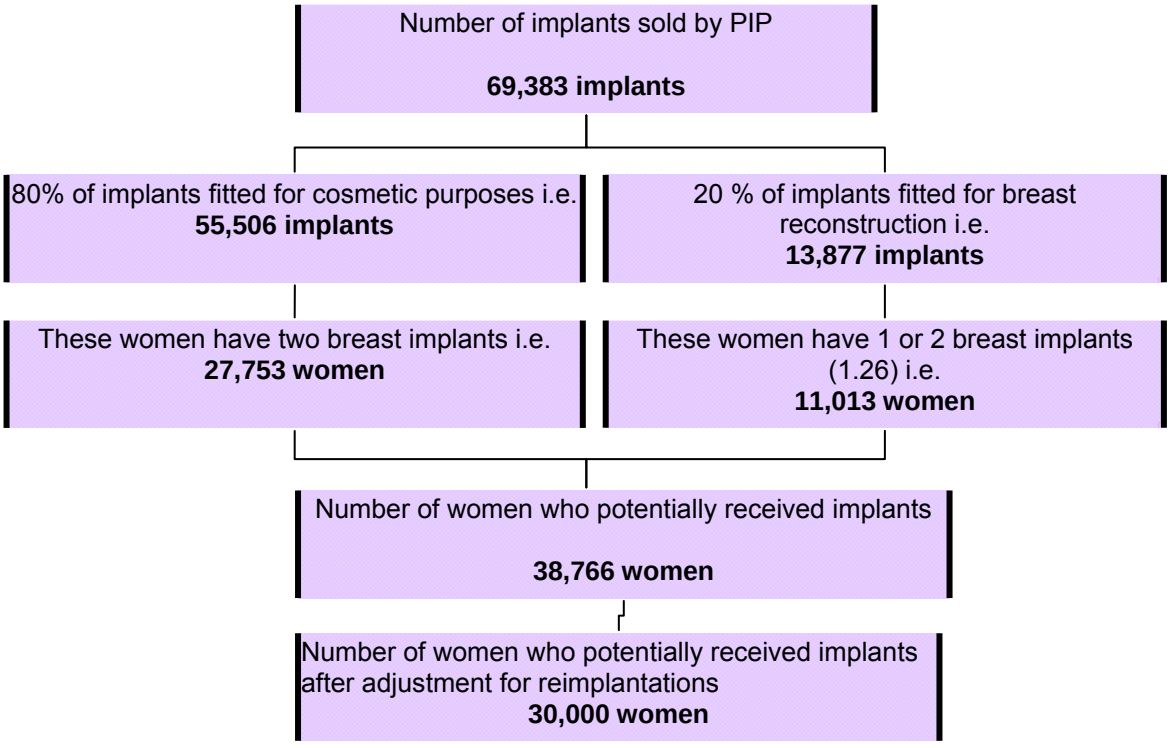

Figure 1. Method of calculating the number of women with implants

By extrapolating from the sales volume (69,383), the number of implants for cosmetic purposes is estimated to be 55,506 (80%) and the number of implants for reconstruction surgery is 13,877 (20%).

For cosmetic purposes, the number of implants fitted per woman is 2, the number of women receiving implants in this indication is therefore estimated to be 27,753.

For reconstruction surgery, the number of breast implants per woman varies from 1 to 2, depending on the case and underlying indication (unilateral or bilateral cancer, for symmetry or not, construction for underdeveloped mammary glands etc). Data collected by the Agency during medical device vigilance indicates that this figure is close to 1.26 implants per woman, bringing the number of women potentially fitted with PIP silicone gel implants in these indications to 11,013.

The total number of women potentially fitted with implants for all indications since 2001 is therefore 38,766. Taking into account the fact that some women have probably had their implants removed once or several tines followed by reimplantation of a PIP breast implants during the period 2001 to 2010, ***the Agency estimated that there were 30,000 women with PIP silicone breast implants at the time of the suspension of marketing on 30 March 2010.***

Based on the data available to ANSM including sales volumes, the Agency considers that there were 30,000 women with PIP silicone breast implants at the time of the marketing ban of 30 March 2010.

1.2 Device vigilance data collected up to December 2012

The appendix summarises the different series of follow-up recommendations for the patients concerned issued from the health policy decision of March 2010 suspending the marketing of implants until the Ministry of Health Recommendations of December 2011 proposing that all women with PIP implants should be offered preventive explantation even if they have no clinical signs of deterioration of the implant.

The data collected by ANSM (Figure 2) indicate that ***14,990 women (25,644 implants) had their PIP silicone gel implants removed between 2001 and December 2012.***

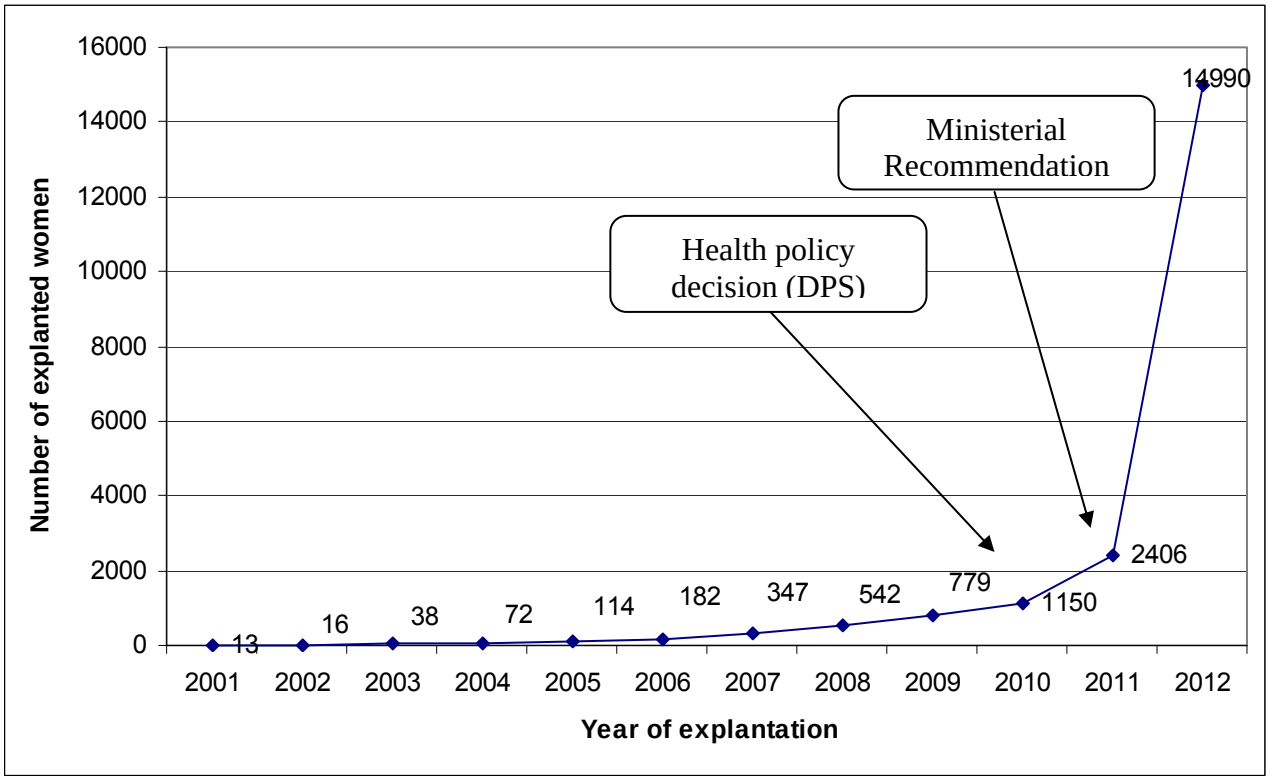

Figure 2. Report of the number of women with PIP implants who underwent explantation reported to the Agency

As in all vigilance systems, there is under-reporting of adverse device incidents, particularly for medical devices used for cosmetic purposes, such as breast implants[1]. A considerable delay in the reporting of incidents has been observed and many reports were collected retrospectively after the health policy decision in March 2010 and in particular, after the media outcry in December 2011. This under-reporting of incidents related to breast implants prior to March 2010 probably led to an underestimation of the number of women explanted before that date. The number of women explanted to date may be higher than the value given above, which corresponds to the cases reported to the Agency and included in the national device vigilance database.

These explantations took place either after a clinical alert sign following clinical diagnosis or imaging (mammography and ultrasound, as MRI is not indicated first-line), or as a precautionary measure decided by the patient.

There are two types of adverse event, breast implant failure or an adverse effect observed in the patient and a same woman may experience both types of event.

> Breast implant failure

Several types of breast implant failure have been reported when taking into account all implants from explanted women (Figure 3). They concern ***6,644 implants (for 5,048 women) and represent 7,042 failure events*** as the same implant can combine several.

The most common are *ruptures* (59% of failures for 63% of implants) and *gel-bleed* (25% of failures pour 26% of implants). These two types of malfunction explain 85% of PIP implant failures.

These failures are not specific to PIP breast implants (all breast implants may present these problems), but their frequency and early occurrence are more important in the case of PIP breast implants.

Other types of failure include:
- Folds, "waves", rotations of the implant,
- Colour changes of the implant,
- Cuts or holes,
- Disintegration and visible defects.

The failure rate of PIP implants is currently 25.9% (6,644/25,644).

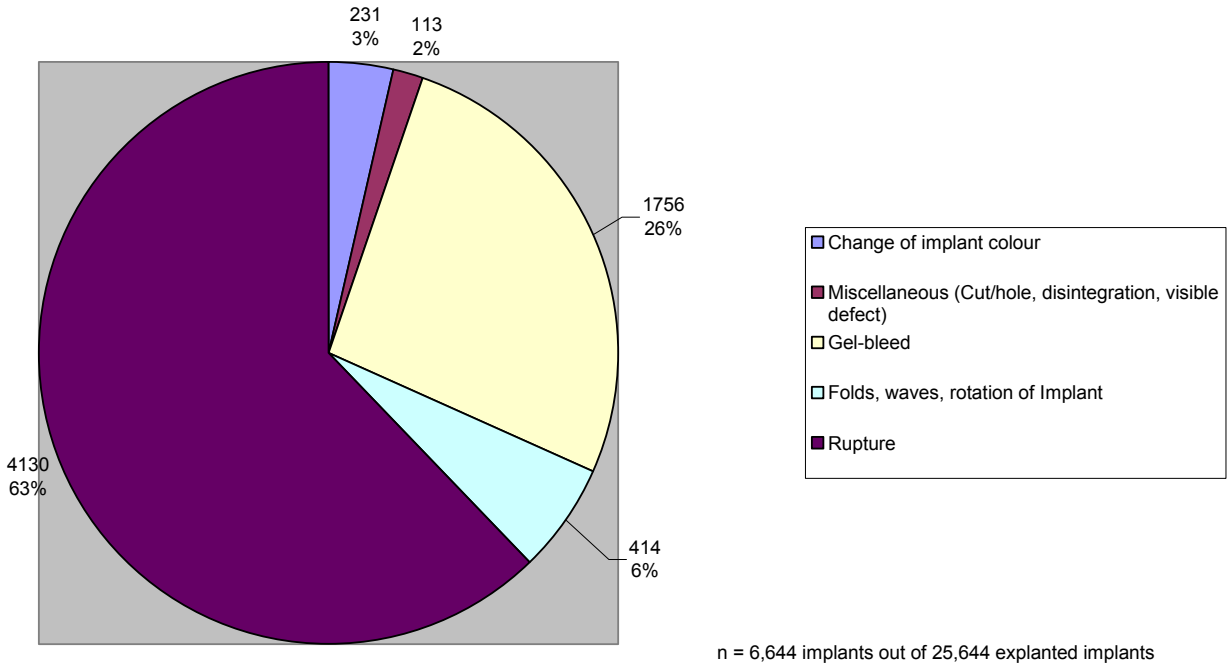

Figure 3. Distribution of implant failures

> Adverse events observed in patients

Adverse effects have also been reported in patients associated or not with an implant failure report. A total of ***4,257*** have been observed in ***2,697 women*** (Figure 4). These are mainly different types of inflammatory reaction. Cases of cancer reported to the Agency are not included in this section and are discussed in a specific paragraph.

The incidence of adverse events with PIP implants observed to date is 16.6% (4,257/25,644).

Capsules represent more than half of the adverse events (48%). Capsular contractures or capsules can have many origins. The analysis of the presence of these capsules is complicated by several factors:

- Notifications by surgeons with difference in the assessment of the capsule stage.
- The incidence of this complication cannot be accurately estimated, since it varies depending on the type, volume and quality of the implant but also on the implantation conditions.
- Variable quality of PIP implants[1].

Siliconomas, lymph node enlargement and lymphorrhoea may be caused by the diffusion of silicone following implant rupture or gel-bleed. These effects account for 25% and may occur in the absence of any visible defects of the implant.

Effusions are the third most common effect (11%). They may be caused by implant rupture or the body's response with secretion of lymphatic fluid.

Finally, inflammation and infection account for 8% of the effects observed in women.

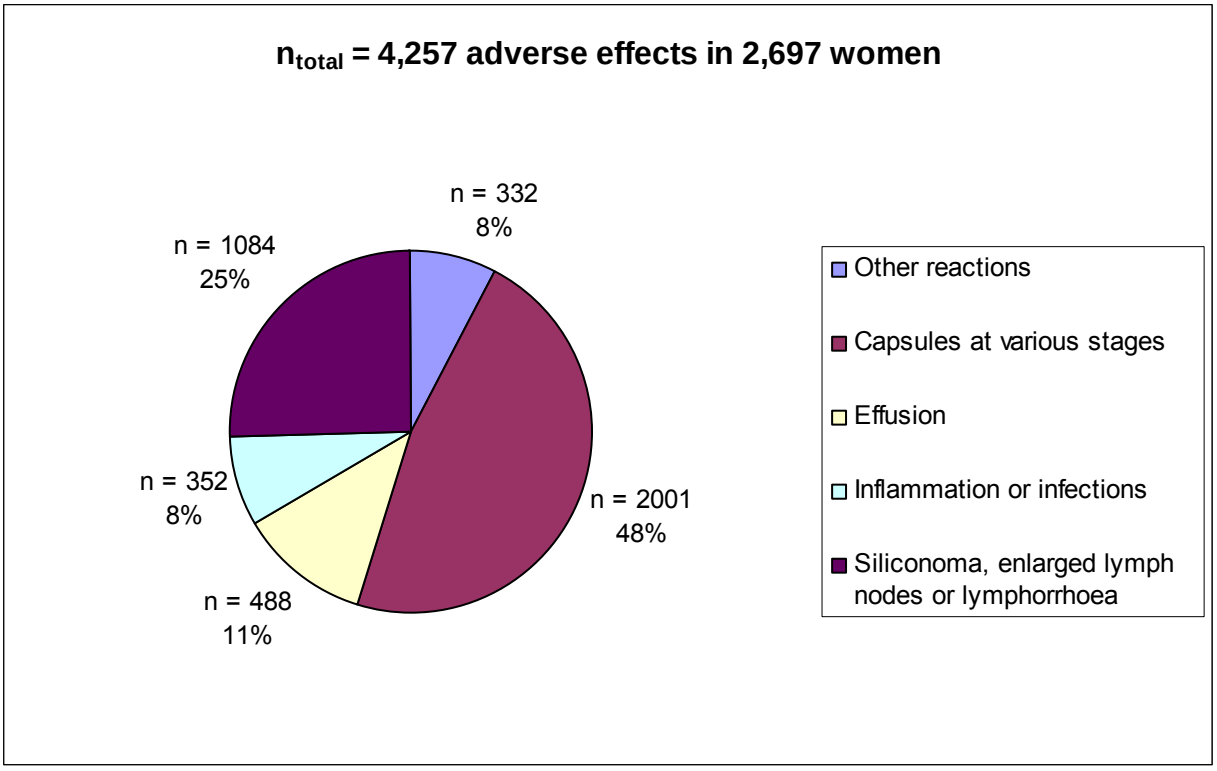

Figure 4. Distribution of inflammatory reactions

From 2001 until December 2012, a total of 14,990 women (25,644 implants) underwent explantation of their PIP silicone gel implants.
There are two types of adverse events, either breast implant failure or an adverse effect observed in the patient, and a same woman may experience both types of event.
A total of 5,048 women had at least one implant failure and 2697 at least one adverse event. These figures may not add up as the same woman may experience both implant failure and an adverse effect.

At this stage of data analysis it is necessary to distinguish between:

- explantations performed after the detection of an implant failure or a clinical alert sign.
- preventive explantation performed without a clinical alert sign and which sometimes leads to the detection of anomalies

All explantations of PIP breast implants, whether preventive or following an incident must be reported to the ANSM. However this information is at the discretion of the reporting surgeon.

1.2.1 Explantations after the detection of an adverse event

This part of the report concerns data reported to the Agency after the detection of implant failure or a clinical sign leading to the explantation of a PIP implant.

At the end of December 2012, ***4061 women had undergone explantation after an alert sign.*** Implant lifespans will be considered separately for women with implant ruptures, the most common failure, and those with adverse effects. The number of women with a ruptured implant cannot be added to the number of women with an inflammatory response, as some women had several adverse events.

1.2.1.1 Implant ruptures

A rupture of the PIP implant with a clinical alert sign or detection during an ultrasound scan was reported to ANSM for **2,703 women, corresponding to a total of 3,263 ruptured implants**, as some women had several implant ruptures

Ruptures were detected at all times after implantation and in particular during the first years after implantation. It is commonly accepted that the life span of a breast implant is 10 years or more. Ruptures detected for PIP breast implants ***occurred after a mean time of 6.3 years (median 5.9),*** which is therefore earlier.

Ruptures (Figure 5) were analysed according to time since implantation for women who had at least one ruptured implant, and for whom information on implant age was available (i.e. 2123 out of 2703)[4].

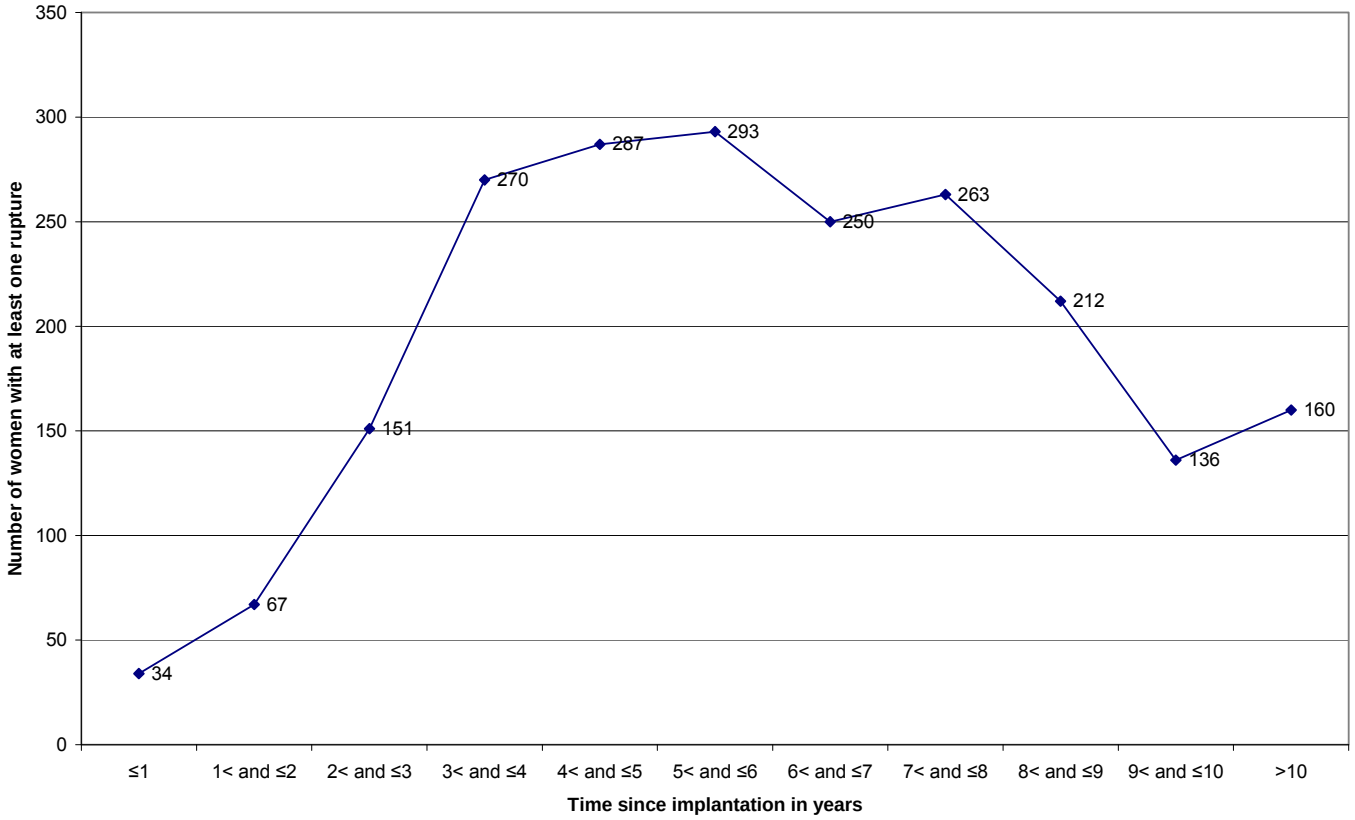

Figure 5. Distribution of the number of women who had at least one rupture

1.2.1.2 Adverse effects

A total of 1726 women whose implant was removed after a clinical alert sign and who presented at least one adverse effect were reported to ANSM***, corresponding to 2276 implants***. These reactions were observed with or without an implant failure report and mainly concerned inflammatory reactions.

These effects were detected regardless of the time since implantation. However, they usually occurred during the first years after implantation at a ***mean implant age of 6.1 years (median 5.9).***

[4] Reports to the Agency did not always mention the dates of implantation and explantation for each implant and both dates are required to calculate the time since implantation.

The effects (Figure 6) were analysed against time since implantation (i.e. 1398 out of 1726).

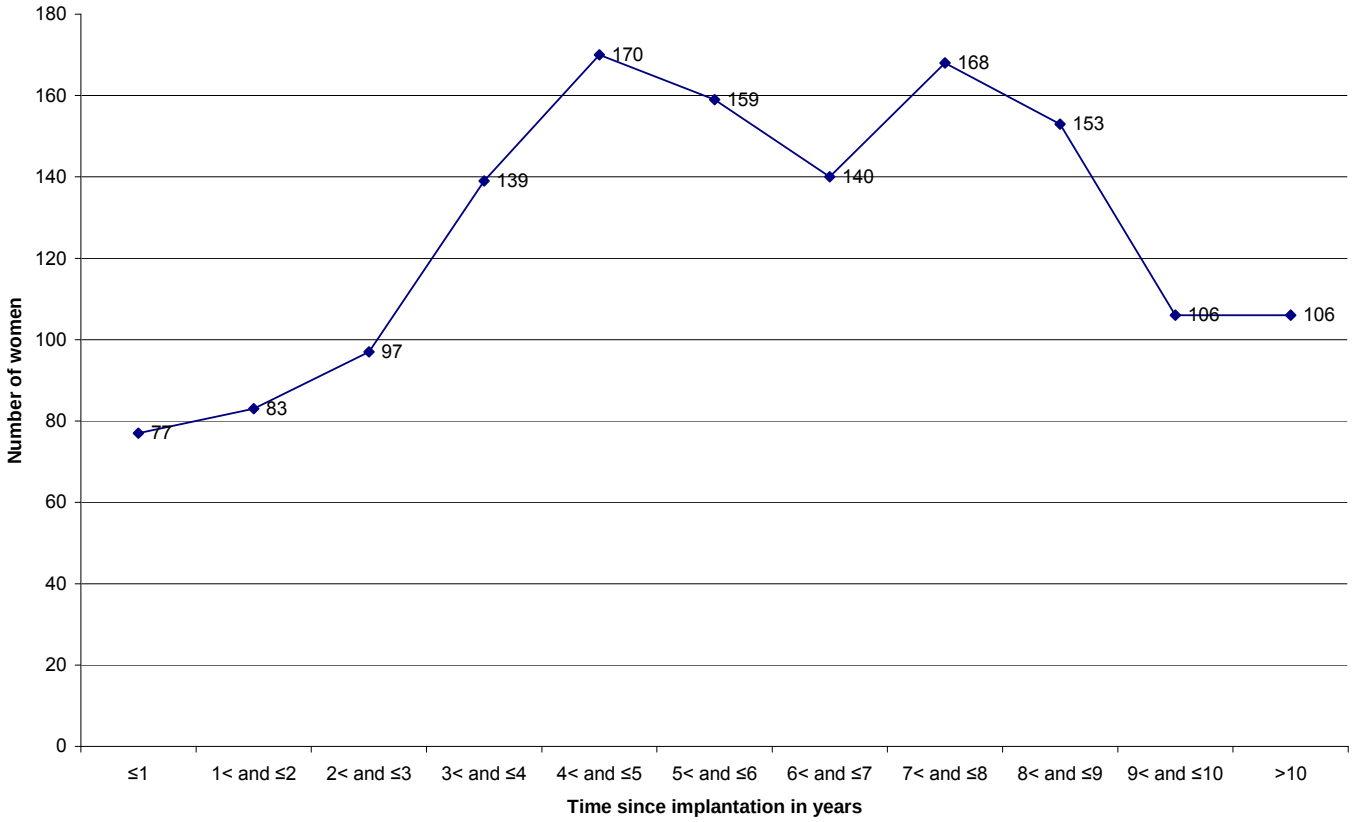

Figure 6. Distribution of the number of women who had at least one adverse effect

At the end of December 2012, 4061 women had had their implant removed after an alert sign.
Rupture of the PIP implant with a clinical alert sign or detection during an ultrasound scan was reported to ANSM for 2703 women, corresponding to a total of 3263 ruptured implants, as some women had several implant ruptures.
A total of 1726 women who had their implant explanted after a clinical alert sign and who presented at least one adverse effect were reported to the ANSM, corresponding to 2276 implants. These reactions were observed with or without an implant failure report.

1.2.2 Preventive explantations since April 2010

1.2.2.1 Total number of preventive explantations

As already mentioned, explantations performed at the patient's request for the removal of the PIP implant are considered to be preventive explantations when no clinical or ultrasound evidence of an adverse event was detected previously.

Before the health policy decision (DPS) of March 2010, there had been 29 preventive explantation reports. These have not been counted in the rest of this section which only concerns preventive explantations performed since the DPS. They were reported in 2009 by the company PIP and no associated adverse events were notified.

Between April 2010 and December 2012, the Agency recorded ***10,900 preventive explantation reports*** including 10,100 with explantation dates indicated by the reporter (Figure 7).

The number of preventive explantations reported during the first 21 months after the DPS was quite low (1743). In December 2011, the Ministry of Health updated the recommendations for

management of women with PIP implants, in particular so that all women with PIP implants, even without clinical signs of deterioration of the implant, are offered preventive explantation[1, 5]. There was then an exponential increase in the number of preventive explantations. The number of preventive explantations reported to the Agency had concerned 4114 women in February 2012 i.e. an increase of 136% over a two-month period. The rythm of explantations continued to accelerate significantly during the beginning of 2012. In June 2012, it was reported that 8445 women had had their implants removed i.e. twice the number of women explanted at the end of February of the same year.

Since the summer 2012, the frequency of these explantations has slowed but remains constant with, at the end of December 2012, a total of 10,900 patients who have undergone preventive explantation including 10,100 with a known explantation date.

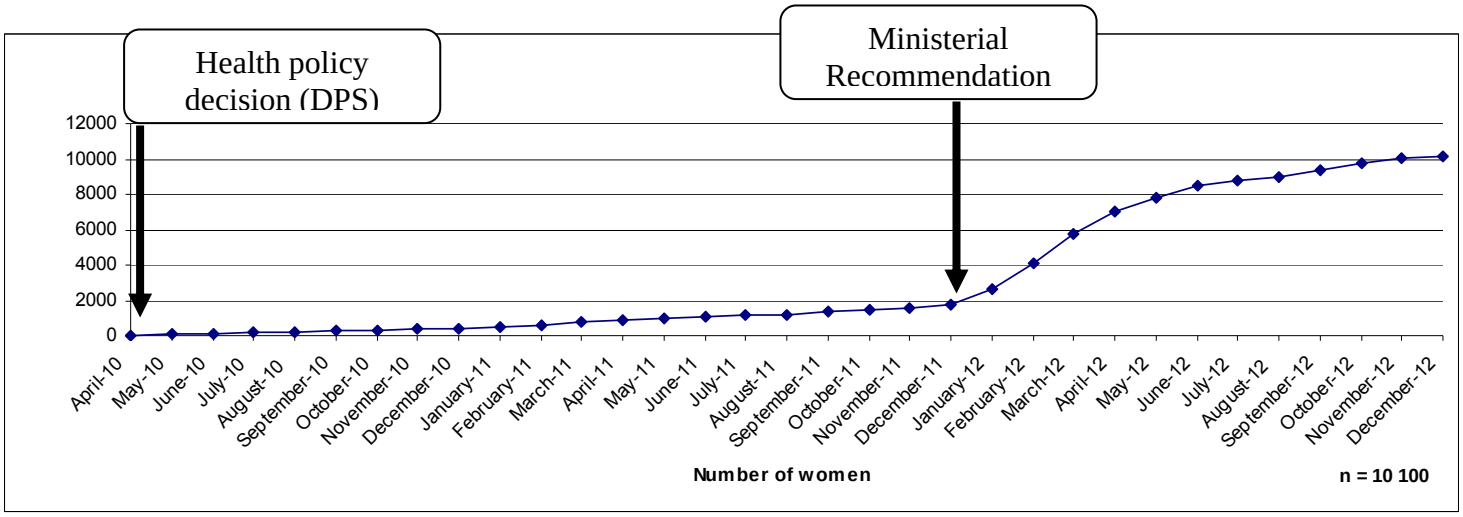

Figure 7. Monthly change in the aggregate number of women who have undergone preventive explantation from April 2010 to end December 2012

[5] http://www.sante.gouv.fr/actualisation-des-recommandations-pour-les-femmes-porteuses-de-protheses-mammaires-poly-implant-prothese-pip.html

> Reports of preventive explantations have shown that for the 10,900 operations performed:

- 8,641 (79%) of women had neither implant failure nor adverse effects.
- 2,259 (21%) of women had an adverse event.

Preventive explantations (Figure 8) were analysed against time since implantation (available for 8,402 women[4]):

- Known time since implantation for 6,602 women out of 8,641 women explanted without adverse events.
- Known time since implantation for 1,800 women out of 2,259 women explanted with an adverse event.

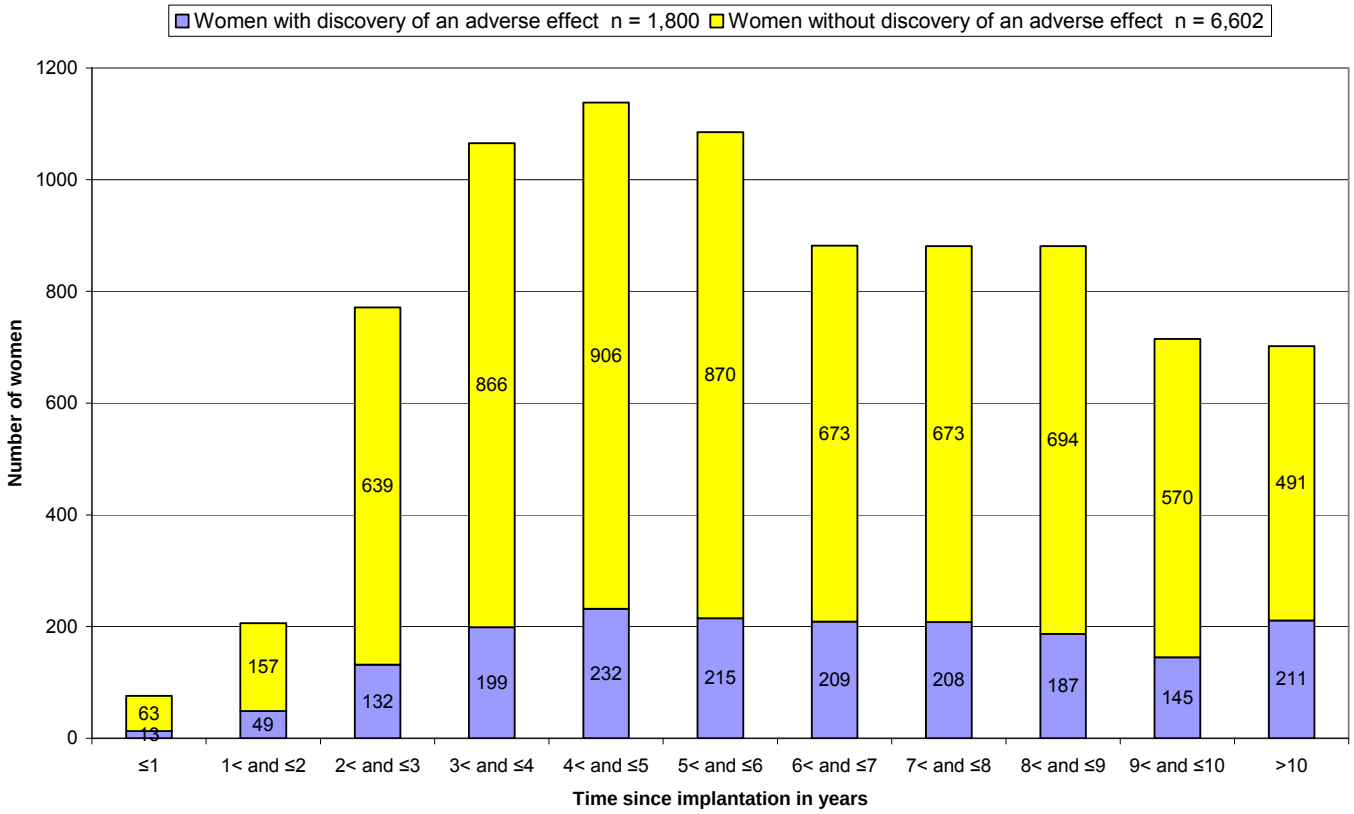

Figure 8. Summary of preventive explantations according to implant age

On average, preventive explantations with no adverse event were performed 6.25 years after implantation, with a median of 6.1 years. It should be noted that these times give a rough approximation of PIP implant survival although they cannot be used to assess their reliability, as these were preventive explantations (without clinical alert signs) and did not follow the occurrence of an adverse event.

For the 10,900 women who underwent preventive explantation (explantations in patients requesting the removal of their PIP implants, without any prior detection of a clinical or ultrasonography sign of an adverse event), 8,641 (79%) women were found to have no implant failure or adverse effect and 2,259 (21%) women had an adverse event.

1.2.2.2 Adverse events discovered during preventive explantation

In 21% of cases (i.e. 2,259 women), implant failure (rupture, gel-bleed etc.) ***and/or an adverse effect undetected*** by the investigations performed before the intervention was in fact observed after preventive explantation.

The actual date of occurrence of these events observed after the operation cannot be estimated as these were preventive explantations. The event may have been silent for several years. Several adverse events were sometimes discovered during explantation.

> Implant failures

These explantation operations revealed the following types of implant failure in the women concerned :

- 692 women had at least one implant rupture,
- 645 women had at least one case of gel-bleed,
- 266 women had at least one other type of failure (change of colour of the gel, implant rotation in the pocket, disintegration of the implant).

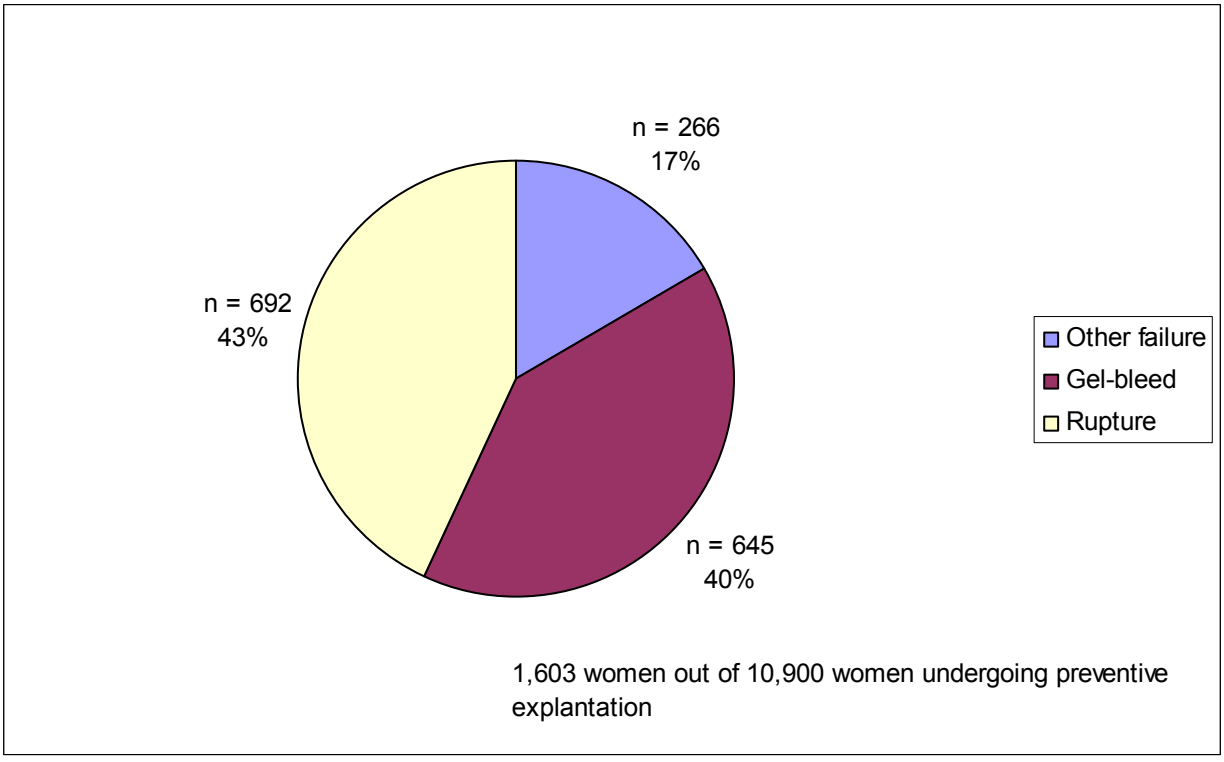

Figure 9. Number of women with implant failure detected during preventive explantation

> Adverse effects observed in patients

In addition, an adverse effect associated (n = 353) or not (n = 618) with an implant failure report was recorded for 971 women.

Capsules represented most of the adverse effects observed in patients with 61% of effects.
Effusions were the second most common effect after capsules.

Lesions or clinical signs affecting the lymphatic system (lymphorrhoea, lymph node enlargement) and siliconomas were the 3rd most common effect in these women.

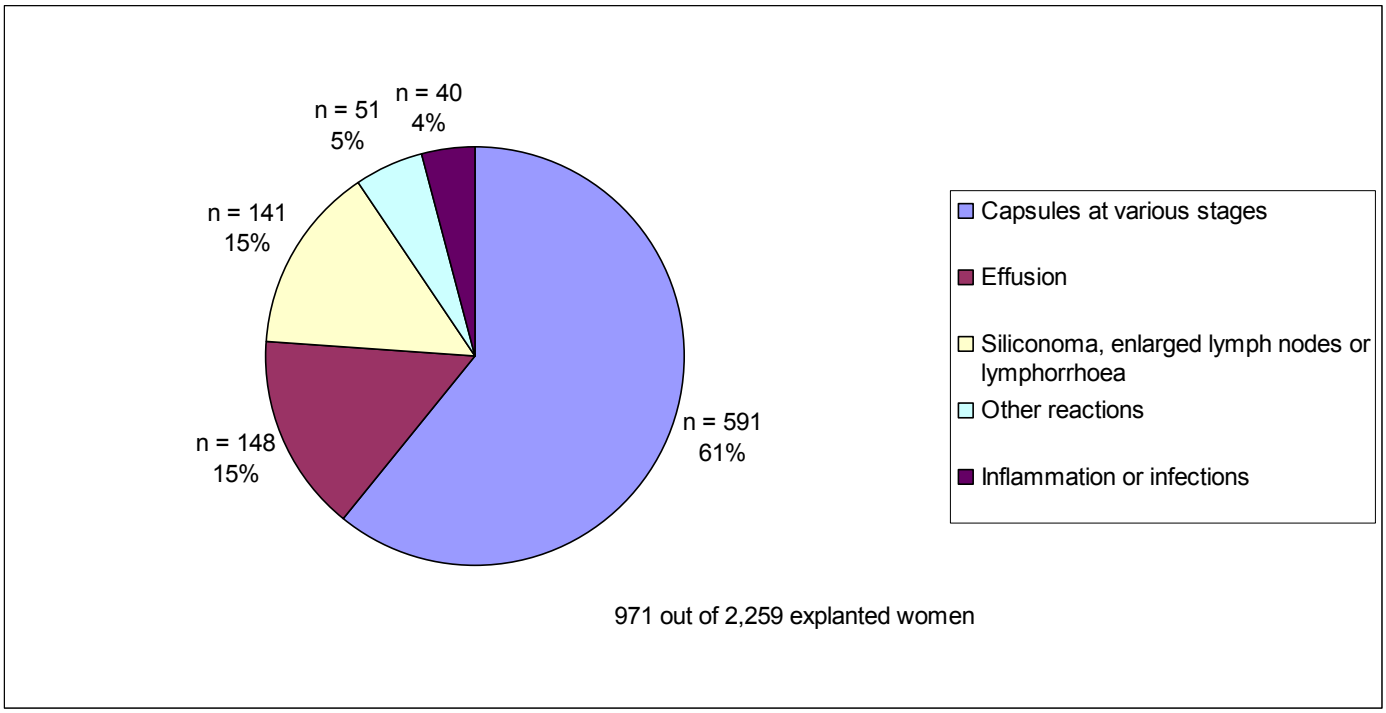

Figure 10. Effects discovered after the explantation of breast implants

Events (implant failures and adverse events) encountered during preventive explantation were detected on average 6.7 years (median = 6.3) after implantation. However, this median time only provides an indication as infraclinical abnormalities may have occurred earlier in the patient's history.

In a total of 21% of cases of preventive explantation (i.e. 2,259 women), implant failure (rupture, gel-bleed etc.) was detected in 1,603 women and/or an adverse effect undetected during investigations performed before the intervention, was discovered in 971 women.

1.2.3 Tumours in women with PIP implants

According to the opinions issued by INCa[6] and experts from the European Commission[2], the reported tumours were not related to any particular characteristics of PIP implants.
One case of anaplastic large cell lymphoma was recorded in November 2011. This report was the reason for the analysis[6] which led to the updating of the recommendations of December 2011.
The agency is not aware of any new cases in women with PIP silicone gel implants.
A total of 64 cases of breast cancer had been reported to the Agency by the end of December 2012 in women with PIP silicone gel implants. These tumours were observed whatever the reason for implantation (cosmetic purposes or breast reconstruction).

[6] Proposed management of women with PIP breast implants: opinion of the INCa expert group, December 2011
"The data available today demonstrate the absence of any excess risk of breast adenocarcinoma in women with implants compared with the general population. There are currently no data demonstrating an increased risk of breast adenocarcinoma in women with PIP implants compared to other implants."
- "There are currently no data demonstrating an increased risk of anaplastic large cell lymphoma in women with PIP implants compared to other implants."

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2. Toxicological data available in France on PIP silicone gels

The data presented are the result of tests and analyses performed in France and described in the report jointly published in February 2012 by Afssaps and the DGS[1] . Data from other countries will be discussed in the third part of this situation update.

The Agency, together with the judicial authorities, has conducted and commissioned analyses of implants taken from the premises of the company PIP. These different analyses were carried out between June and early September 2010, according to the applicable standards for breast implants. Their purpose was to characterise both the raw materials used and the mixtures forming the gel filler, determine the resistance of the implants and finally to evaluate the tolerance of biological tissues in contact with the gel filler. This final point was complemented by a second series of biological tests in early 2011.

> Physical, chemical and mechanical tests:

- Identification of the raw materials used to manufacture the gel fillers

  - Determination of the numerical mean molecular weight and the dispersion index of polymers by high pressure liquid chromatography (HPLC)
  - Identification and assay of low molecular weight silicones by gas chromatography-mass spectrometry (GC/MS) in comparison with reference standards

- Study of the release of silicone by the implant

  - Release of silicone performed by emission spectrometry according to standard NF/EN/ISO 14607/2009.
  - Determination of sweating (see ASTM standard F703/2007) in order to monitor the gain in weight of the silicone disc due to gel-bleed of the test implant over an eight week period.

- Characterisation of the mechanical properties according to standard NF EN ISO 14607, based on the results of the following tests:
  – Tensile strength test
  – Fatigue resistance test
  – Elongation at break test
  – Static breaking strength test (No performance criterion is defined in the standard)

> Toxicological studies on the finished products:

Tolerance tests of biological tissues in contact with the filler gel performed according to standard NF EN ISON 10993 including:

- an *in vitro* test assessing the toxicity for cells (cytotoxicity)
- an *in vivo* test evaluating intradermal irritation (in the rabbit)
- several tests evaluating the harmful effect of the gel on cell DNA (genotoxicity)
  - an *in vitro* assay (Ames reverse mutation test on bacteria)
  - an *in vitro* chromosomal aberration test on human lymphocytes
  - an *in vivo* micronucleus test on mouse erythrocytes
  - an *in vivo* comet assay on mouse liver

> Summary of the analyses and tests performed in France

The physicochemical tests performed on implants sequestered on the Poly Implant Prosthèse site made it possible to confirm the **presence of a different gel filler to that declared in the CE marking technical file** ("NUSIL" gel). The results of analysis and examination of the texture of gels extracted from implants showed that "***PIP" gel formulations are of poor quality*** (in particular because of the presence of high levels of D4-D13 siloxanes), in terms of crosslinking, reproducibility and the physical and chemical properties of the gels.

Mechanical tests showed **non-compliance with the standard** for the elongation at break test for textured implants and, in general, a poorer quality of textured implants in comparison with smooth implants which nevertheless had a heterogeneous quality.

The documented variability of the physical and chemical properties of PIP gel between batches is a major obstacle to the characterisation of a toxicological profile that can be extrapolated to all of these implants.

Within the scope of risk assessment for patients exposed to these gels, it is first necessary to consider the results of the **intradermal irritation test** in rabbits showing the non-compliance of all the gels tested (4 batches) which had a mild to moderate irritant potential. The induction of an inflammatory reaction under the experimental conditions of this test is consistent with the reports of chronic inflammatory reactions observed in some implanted women. The existence of a local chronic inflammatory reaction is a recognised risk factor for cancer [19-24], although this risk has not been experimentally demonstrated to date in the case of PIP gels.

Under the experimental conditions used to perform the **genotoxicity studies**, a negative or doubtful genotoxic effect was observed depending on the type of study performed on the batch of gel tested. However, taking into account the methodological limitations of these studies and the variability between batches clearly shown by the physicochemical tests, no overall conclusion about the genotoxicity of "PIP gel" can be made. Each batch appears to be unique. Given the significant heterogeneity of the batches of gel used to fill the implants manufactured by PIP, it is impossible to determine if "PIP gel" has a specific genotoxicity. Finally, the genotoxicity does not alone determine the carcinogenicity of a product.

However, the non-compliance, defective quality, variability from one batch to another and irritancy are four findings which alone justify the precautionary surveillance of women with implants and even the explantation of these implants.

It is unlikely that new genotoxicity tests would provide any more relevant information to assess this risk. The only way to investigate the carcinogenic risk of these gels on the basis of experimental data would be to conduct carcinogenicity studies under in vivo implantation conditions as close as possible to those used in implanted women. However, considering the relatively small number of implants made from a single batch of gel and the variability between batches, it would be extremely difficult to extrapolate the results obtained in these studies to all PIP implants. Risk analysis both at individual and population level has therefore proved extremely difficult and there seems little point in continuing it, all the more so when decisions have already been taken about surveillance of women and explantation.

In addition and as explained in the following sections, the available international toxicity data corroborate the information obtained in France.

3. International data

PIP implants have been sold worldwide, particularly in the United Kingdom and Australia. These countries have carried out their own analysis of PIP implants, and also reported their findings on PIP. Following the AFSSAPS alert after the inspection of PIP, the European Commission asked the SCENIHR[2] to draft a report on the safety of PIP implants. This was published in February 2012 and is based mainly on the French data.

3.1 Vigilance data in other countries

3.1.1 United Kingdom

In December 2011, following the reinforcement of the French recommendations, the English Secretary of State for Health asked the NHS (National Health Service) Medical Director to set up an expert group to conduct a study on the safety of PIP implants. The group released an interim report[7] in January 2012 and a final report in June 2012[8].

In addition, in May 2012, the MHRA published a review[9] of its actions concerning PIP silicone breast implants.

Concerning the data notified by the vigilance system[9] before the French decision of March 2010, the MHRA reported that there were no conclusive data showing any problem with PIP implants but that a small number of implants failed more rapidly than other types of implants. In addition, the MHRA made the same remark about the under-reporting of incidents as in France.

A retrospective analysis was conducted on explanted PIP implants and other implants over the period 2001-2011[8].

According to data provided by sites fitting breast implants, PIP implants were implanted in 26,000 of the 131,000 women (238,000 implants) who received implants.

There were 5,870 explantations of breast implants, 1,565 of which concerned PIP implants.

During these explantations it was found *that 31.1% (486/1,565) of PIP implants had defects (ruptures and gel-bleed) versus 4.3% (186/4305) for other brands of implants.*

The conclusions of this retrospective analysis are presented in the final report of the group of experts[8] together with the limitations that led to an underestimation of the observed incidence of adverse events (implant defects or local clinical signs):

- *PIP implants presented 2-6 times more failures (ruptures and gel-bleed) than other brands of implants, and this difference was already clear 5 years after implantation*
- *The implant failure rate (rupture and gel-bleed) for PIP was estimated to be 1.2% at 5 years and 3.1% at 10 years versus 0.2 to 0.4% at 5 years and 1.1% at 10 years for other breast implants.*
- *PIP implants induced 3-5 times more local clinical signs than other implants. The incidence rate of clinical signs was 0.8% at 5 years and 2.1% at 10 years*
- *PIP implants are not associated with an excess risk for other clinical problems such as capsular contracture, haematoma and cancer.*

[7] PIP breast implants: interim report of the Expert Group, NHS, (DH, January 2012)
[8] PIP breast implants: final report of the Expert Group, NHS, (DH, June 2012)
[9] Poly Implant Prothèse (PIP) silicone breast implants "Review of the actions of MHRA and Department of Health", May 2012

3.1.2 Australia

Non-implanted PIP prostheses were recalled in Australia in April 2010, following the AFSSAPS decision.

The TGA estimated that about 13,000 PIP silicone gel implants were delivered to the Australian market between 1998 and 2010.

The number of women who received PIP implants was estimated to be 5,000 by the TGA as most women were operated for cosmetic purposes and therefore received two implants.

The number of women who actually received implants is unknown.

On 31 January 2013, the TGA has received 473 reports of rupture of PIP breast implants (451 of which were confirmed and 22 unconfirmed [10]).

Figure 11 shows the number ruptures versus time since implantation when this was known (265 of 473). The data reported to the TGA suggest *that ruptures occur on average between 5 and 6 years after implantation.*

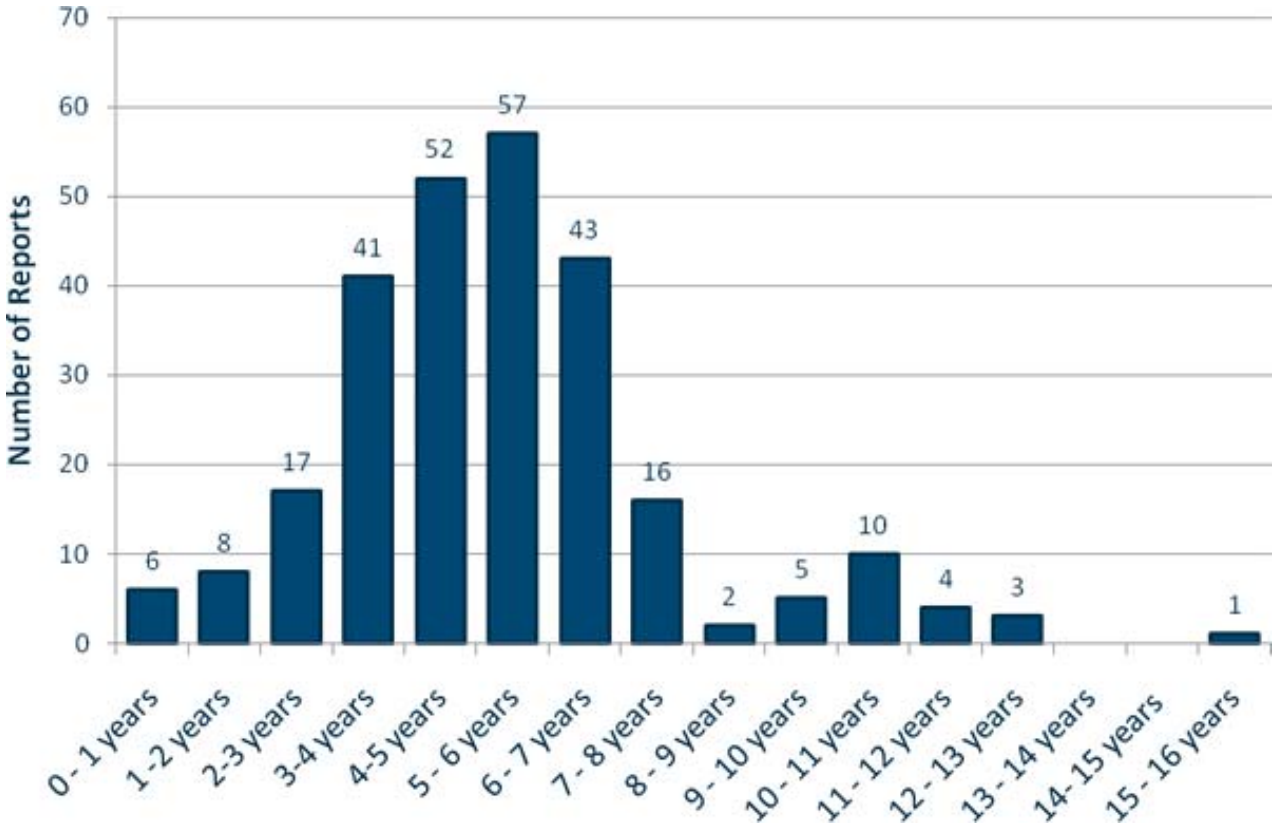

Figure 11. Distribution of implant ruptures versus time since implantation

A report published in April 2012[11] by the Australian Department of Health concluded that *the rupture rate of PIP implants is higher than for other silicone implants.*

In addition, no cases of anaplastic large cell lymphoma have been reported in Australia.

[10] http://www.tga.gov.au/safety/alerts-device-breast-implants-pip-130211.htm#reports

[11] Poly Implant Prothèse (PIP) Breast Implants: Report of the Chief Medical Officer, Department of Health and Ageing, April 2012

3.1.3 Discussion and summary of the French and international vigilance data

The English, Australian and French data are consistent. ***The implant failure rate (rupture and gel-bleed) is higher for PIP implants compared to other implants from the first years after implantation.***

In addition, both the MHRA and the French Authority pointed out the under-reporting of incidents occurring with breast implants in general and therefore the potential impact in the PIP case. The accurate reporting of this information is essential in order to detect trends in the frequency of occurrence of incidents that are expected to occur such as ruptures.

Following the first SCENIHR[2] report in February 2012 mentioning in particular the lack of available data on reported incidents, the European Commission requested an update[12] of this first report and asked the SCENIHR in particular to help create a European questionnaire for the different Member States in order to collect data on patients with implants. The results should soon be available.

Cancer and anaplastic large cell lymphoma.

To recap, the French National Cancer Institute (INCa), concluded on 23 December 2011 that:

"The data available today demonstrate the absence of any excess risk of breast cancer in women with implants compared with the general population. There are currently no data allowing us to conclude that there is an excess risk of breast cancer specific to PIP implants compared to other implants."

- "There are currently no data demonstrating an excess risk of anaplastic large-cell lymphoma specific to PIP implants compared to other implants."

Likewise, in its report of 1/2/2012, the SCENIHR Scientific Committee mobilised by the European Commission also considered that there are no data suggesting an increased risk of lymphoma or breast cancer in patients with PIP implants[2] . These conclusions were taken up by both the English and Australian authorities.

In France one case of anaplastic large cell lymphoma was reported in a woman with PIP breast implants.

In January 2011, the FDA had identified worldwide 60 cases associated with breast implants, including 34 documented cases with a breast location (including 17 in the U.S.). This particular type of lymphoma is very rare among all lymphomas: according to the American National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) programme, it can be estimated that one woman in 500,000 develops this type of lymphoma each year in the U.S. The breast location for this type of lymphoma is even rarer with an estimated yearly incidence in the U.S. of 3 cases per 100 million women.

Considering that nearly 4 million women received breast implants in the United States between 1998 and 2009, the FDA believes that in the United States, the incidence of anaplastic large cell lymphoma is higher in women with breast implants that in the epidemiological data observed for the general population.

[12] Request for an update scientific opinion on the safety of PIP silicone breast implants
http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_q_031.pdf

Concerning anaplastic large cell lymphoma, the FDA concluded in January 2011 that:

1. The association of this type of lymphoma with implants was "possible", given the fact that in the reported cases the tumour mainly occurred in areas close to the implant;
2. It is currently impossible to reliably link this serious event to a particular type of implant;
3. The pathophysiological cause of this serious event has not been established to date;
4. Given the extremely low frequency of this type of lymphoma and the evidence gathered to date on breast implants, the safety of these products is not questioned.

European and international studies are currently in progress to obtain more precise data.

3.2 International toxicological data

3.2.1 United Kingdom

In September 2010, in parallel with the tests conducted by Afssaps, the MHRA commissioned a first series of tests[13] to evaluate the toxicity of PIP silicone breast implants and then completed this evaluation in 2012 by a second series of tests[14,8]. All these tests were conducted under *in vitro* conditions by comparison with implants filled with medical grade silicone gel.
The following series of tests was performed:

- Comparative composition of PIP implants and implants with medical grade silicone gel
- Genotoxicity tests *(in vitro* Ames assay: bacterial reverse mutation)
- Evaluation of cytotoxicity (in vitro test on fibroblast cultures) ,
- Skin irritation test (*in vitro* test on the EpiSkin model)

The results concerning implant composition, such as those of tests commissioned by the French authorities, showed that concentration levels of low molecular weight D4-D6 siloxanes were significantly higher (10 times or more) in PIP implants than in medical grade silicone implants, and that these levels varied from one batch to another.

PIP silicone implants do not contain major levels of organic or inorganic impurities. Platinum levels (catalyst used in the polymerisation of the gel) in PIP silicone gel implants are lower than in medical grade silicone implants. A very low level of caesium was detected in PIP implants unlike in medical grade silicone implants.

Moreover, low molecular weight siloxanes were assayed in the milk of a woman with ruptured PIP implants. The quantity detected was much lower than that found in commercial cow's milk.

Concerning the toxicological data, the MHRA concluded that the *in vitro* evaluation of the toxicity of the gel demonstrated no genotoxicity or cytotoxicity, supporting the French results.

In addition, the PIP implants tested were considered to be non-irritant according to an *in vitro* skin irritation test on the EpiSkin skin model.

Finally, the MHRA[13] and NHS[8] reports point out that the presence of these siloxanes is not a significant health risk for subjects with implants even in the case of the complete rupture of the implant. Siloxanes are not genotoxic and do not cause skin or eye irritation or allergic sensitisation

[13] Summary report on tests performed on extracts of silicone gel filler material from PIP silicone breast implants, Sept. 2012
[14] Chemical analysis summary, composition and toxicity of PIP silicone, November 2012

or induce acute toxicity. D4 siloxanes were shown to reduce female fertility in rats under exposure conditions corresponding to the inhalation of 300 ppm or more. However, this is not considered to represent a risk for human health.

In view of all these results, the MHRA and NHS concluded that PIP silicone breast implants differ from medical grade silicone by a higher concentration of siloxanes. This does not represent a risk to human health.

3.2.2 Australia

The Australian authority carried out several series of tests and analyses from 2010 until the last update in February 2013[15].
Overall, the TGA commissioned the following tests:

- Chemical and physicochemical analysis of the composition of the gel and shell
- Mechanical tests according to standard EN ISO 14607 for evaluating the tensile strength of the shell and cohesiveness of the gel
- An *in vitro* test to evaluate the cytotoxicity of the filling gel according to ISO 10993-5
- Transdermal irritancy test according to ISO 10993-10: 2010
- Visual inspection and mechanical testing of explants

The results of these tests showed:

- The absence of volatile organic compounds among a selection of compounds (10 different batches) and trace metals
- The presence of D4-D6 siloxanes in implants in proportions broadly consistent with the results obtained by Afssaps and unrelated to the year of manufacture
- The compliance of PIP implants tested according to the requirements of the standard on mechanical tests (15 samples from 13 different batches)
- Negative results on cytotoxicity for all the implants tested (8 samples from 5 different batches)
- Negative results in intradermal irritation tests in rabbits when the same series of tests was performed by two different laboratories (7 batches)
- Visual examination of explants showed damage to the shell, a lack of cohesiveness and a change of colour for certain products and the mean elongation at break of explanted PIP breast implant shells was about 35% lower than for non-implanted samples of smooth and textured shells.

This latter observation was expected, since it had already been reported for breast implants produced by other manufacturers [16,17] .

TGA results on explants therefore confirmed the previously published scientific data: the mechanical resistance properties of silicone breast implants deteriorate after implantation in the human body.

The report published in April 2012[11] by the Australian Department of Health concluded that the tests conducted by the TGA did not identify any specific safety issue with PIP implants. In particular, although the presence of low molecular weight siloxanes is a marker of non-

[15] http://www.tga.gov.au/safety/alerts-device-breast-implants-pip-130211-testing.htm
[16] Brandon HJ, Young VL, Jerina KL, Wolf CJ, "Analysis of explanted silicone/silica composite breast implants" Advanced Composites Letters 9 (2000) 115
[17] Marotta JS, Goldberg EP, Habal MB, Amery DP, Martin PJ, Urbaniak DJ, Widenhouse CW. "Silicone gel breast implant failure: evaluation of properties of shells and gels for explanted prostheses and meta-analysis of literature rupture data". Ann Plast Surg 49 (2002) 227

compliance, this does not pose a safety problem. Finally, they underlined the differences with the French results for the intradermal irritation test and elongation at break test.

3.2.3 Discussion and summary of the French and international toxicological data

All the tests performed in France, the UK and Australia led to the same conclusions that these implants do not result in any significant risk to human health and in particular have no cytotoxicity or genotoxicity.

The physicochemical tests gave concordant results demonstrating in particular the heterogeneity of batches of PIP implants and the presence of **higher levels of siloxanes** (D4-D6) compared to other breast implants and in particular those manufactured according to the CE marking dossier. These low molecular weight molecules are therefore markers of the non-compliance of these implants, leading in particular to their fragility and tendency to bleed, although they are not considered to constitute a significant health risk. There are no other organic or inorganic impurities in PIP implants.

One of the two conflicting results concerned the *in vivo* intradermal irritation test performed according to ISO 10993-10 which gave negative results in the Australian tests whereas the gel was slightly to moderately irritant in the tests performed in France. The French results are corroborated by the reports of inflammatory reactions. Moreover, these discrepancies may be partly explained by the known variability between batches.

4. Conclusion in 2013 and ANSM action plan

French and international medical device vigilance reports and the physicochemical and toxicological data on PIP implants are concordant.

Follow-up recommendations for women vary according to the country. The French authorities have recommended that as a precautionary and non-urgent measure, the women concerned should be offered the explantation of their implants even if there is no clinical sign of damage to the implant.

In parallel with the ongoing work of the SCENIHR[12] and the other countries, ANSM continues to pursue a plan involving specific actions and increased surveillance of breast implants in France.

1. The adverse device incident reports with PIP implants will continue to be subject to specific monitoring, including periodic updates which will now be published three times a year.

2. Surgeons will be asked to repeatedly inform their patients about the need for monitoring: an assessment of explantations has shown that implant failures or other adverse events were fortuitously detected after preventive explantation (no clinical alert sign) in 21% of these women. It is now estimated that more than half the women with PIP implants have been explanted. However the other women should be further informed about the importance of clinical and radiological follow-up and reminded about the preventive explantation option.

3. Surveillance of all other silicone breast implants, as well as for PIP implants which were withdrawn from the market in 2010, has been stepped up: in particular the Agency has implemented an inspection programme to control all the implants sold in France. In addition, work is under way to facilitate the setting up of a register for the follow-up of the patients concerned.

The ANSM continues to monitor any new data and will take into account any finding, including from the next review conducted by the SCENIHR, which may make it necessary to update the follow-up recommendations for women with PIP implants.

APPENDIX

History of recommendations for the follow-up of women with PIP breast implants.

Follow-up recommendations for women with PIP silicone gel breast implants have been reviewed and updated each time new information has been obtained since the health policy decision of March 2010[1].

30 March 2010: Afssaps recommendations

Within the framework of follow-up of women with these implants, Afssaps asked surgeons to make an appointment with women in whom they have implanted PIP silicone gel implants in order to give them this information and prescribe an ultrasound scan to check the implant within a maximum timeframe of six months.

28 September 2010: Updating of Afssaps recommendations

In September 2010, Afssaps recommended as a precautionary measure, to increase the frequency of follow-up of women with PIP implants so that each may have a clinical examination with an ultrasound scan during a period of less than 6 months. It was also recommended that if an implant rupture was detected or suspected during these examinations, both this implant and the second breast implant should be explanted. Finally, it was stated that the next contact between the surgeon and patient would provide an occasion to discuss possible explantation even in the absence of any clinical evidence of deterioration of the implant.

15 April 2011: Updating of Afassaps recommendations

In April 2011, after publishing the results of additional tests, Afssaps maintained its previous recommendations and specified that according to vigilance data, a clinical examination and ultrasound scan every 6 months should target both breast and axillary lymph node regions, and that the implant should be explanted if gel-bleed of the gel was suspected. It was also recommended after explantation of an implant showing unusual signs of inflammation, to take a histological and immunohistochemical specimen on the capsule.

30 November 2011: Updating of Afssaps recommendations

In November 2011, following the case of anaplastic large-cell lymphoma occurring in the breast of a patient with PIP implants, Afssaps reiterated and clarified its recommendations of April 2011, namely:

- Patients should routinely undergo a clinical examination and ultrasound scan every 6 months, targeting the breast and axillary lymph node areas during each of these examinations;

- Any rupture, suspected rupture or gel-bleed from an implant should lead to the explantation of both this implant and the second breast implant.

- "Anaplastic large-cell lymphoma of the breast should be considered in particular in the case of persistent periprosthetic serous effusion occurring after implantation surgery as well as in certain cases presenting capsular contracture or masses close to the serous effusion".

- Afssaps asked professionals to advise patients and discuss with them the possibility of explantation even if they present no clinical evidence of deterioration of the prosthesis. This choice should be made after evaluation with the surgeon of the individual risk/benefit ratio including the risk of complications inherent to the procedure.

23 December 2011: Updated recommendations of the Ministry of Health intending to reinforce those issued by Afssaps and recommendations of the experts convened by INCa

The following instructions were sent to regional health agencies by the DGS and DGOS:

- Women with breast implants should check the brand of their implant on the implant card they were given. If they have no such card, they should contact their surgeon or the institution where the implantation was done.

- Patients with PIP implants should consult their surgeon. They will then be proposed preventive explantation, even if they present no clinical sign of deterioration of the implant. If they do not wish to have their implant removed, they should have a follow-up ultrasound scan every 6 months, targeting breast and axillary lymph node areas.

- Any rupture, suspected rupture or gel-bleed from an implant should lead to its explantation, as well as the second breast implant.

- Prior to explantation, for whatever reason, an imaging assessment (including a mammography and a breast and axillary ultrasound scan) must be available.

- To ensure that any woman who wishes to have her implants removed can do so, ministry officials have requested that all Regional Public Health Agencies (ARS) set up, from the beginning of January, a hotline for women with PIP breast implants who may have difficulties reaching a healthcare professional in order to propose a list of institutions able to treat them.

- Health care facilities and health professionals were informed at the same time about this decision and the new recommendations.

- Any costs associated with explantation, including the hospital stay, will be covered by national health insurance. In the case of women who have had reconstructive surgery after breast cancer, the implantation of a new implant will also be reimbursed.