afssaps
Agence française de sécurité sanitaire des produits de santé

# TOPICAL REPORT
# PIP SILICONE GEL PRE-FILLED IMPLANTS

## 1- Context of the health policy decision dated March 29, 2010

**The Afssaps detected, in the framework of its medical device vigilance function, in the last quarter of 2009 an increase in the number of ruptures of breast implants pre-filled with silicone gel manufactured by the company Poly Implant Prothèse. Following these reports and several unsuccessful exchanges with the manufacturer, the Agency carried out an inspection in the premises of this Company between March 16th 2010 and March 18th 2010, which revealed the use of a silicone gel different from the one that had been declared for the placing on the market.**

**Regarding these elements, the Afssaps decided to suspend the placing on the market (1) and the use of PIP breast implants pre-filled with silicone gel on March 29th 2010. This health policy decision (HPD) was made public on March 30th 2010 (2 and 3). This decision was accompanied of recommendations for the attention of surgeons and women implanted with PIP silicone breast implants.**

Independently, the PIP Company filed for bankruptcy in March 2010, which means that no PIP implants can be marketed any longer. Since this decision, the PIP Company has been taken over. However, the takeover Company to market breast implants, must comply with the regulatory procedures prior to any placing on the market.

Since 2001, when the silicone gel implants were reintroduced on the French market, approximately 30,000 women have been implanted with PIP prostheses, **i.e. approximately 6% of** women with silicone breast implants, estimated at 500,000 in France.

**Also read**
(1) Decision dated March 29th 2010 concerning the withdrawal and suspension of the marketing, distribution, export and use of breast implants pre-filled with silicone manufactured by the company POLY IMPLANT PROTHESE (30/03/2010)
(2) Letter for the attention of the health establishments and surgeons concerned - Information/Recommendation (30/03/2010)
(3) Press release: Silicone gel breast implants from the company Poly Implant Prothèse (30/03/2010)

## 2- Tests performed on PIP silicone gel breast prostheses

The Afssaps performed and sponsored, jointly with the legal authorities, some analyses on the implants taken from the premises of the PIP Company (4 and 5). These analyses were performed between June and beginning of September 2010 according to the standards applicable to breast prostheses. Their objective was both to characterise the raw materials used and the mixtures making up the filling gels, determine the resistance of the prostheses and finally to assess the tolerance of biological tissues in contact with the filling gel. This last point was completed by a second series of biological tests (6) performed at the beginning of 2011.

The physico-chemical analyses, performed at the Chemistry School of Montpellier and the laboratories of the control test department of the Afssaps, confirmed that the gel filling the breast prostheses taken at PIP are not those described in the manufacturer's dossier. It is a gel made of compounds from the silicone family; however this gel does not reach the required degree of quality of a silicone gel intended for breast implants. Furthermore, the tests performed on the different batches of breast implants revealed a non-reproducibility of the processing.
The characterisation of the mechanical properties was performed by the National Test Laboratory according to the NF EN ISO 14607 specification from the results of the following tests:
- tensile test
- fatigue resistance test
- tear elongation test
- static rupture resistance test (no performance criterion indicated in the specifications)

The results of the tensile set and fatigue resistance tests comply with standards. The tear elongation test does not comply. This result demonstrates a fragility of the shells filled with PIP gel.

The results of the physico-chemical and mechanical properties analyses also reveal a major heterogeneity of the quality between prostheses.

The tolerance of biological tissues in contact with filling gel tests performed by the laboratories of the control tests department of the Afssaps, the laboratory BIOMATCH and the Lille Pasteur Laboratory in compliance with the NF EN ISON 10993 standards include:
- an in vitro cell toxicity evaluation test (cytotoxicity)
- an in vivo (in rabbits) intra-dermal irritation evaluation test
- several tests to evaluate the effect of the gel on cellular DNA alteration (genotoxicity)
    - In vitro Ames test (reverse mutation in bacteria)
    - In vitro chromosome aberration test in human lymphocytes
    - In vivo micro-nucleus tests on mice erythrocytes
    - In vivo Comet assay in mice

The results are the following:

- the gel from PIP breast implants does not present any acute toxic effect on tissues (cytotoxicity).

- the results of the intra-dermal irritation tests performed show an irritant potential of the PIP gel not found with the silicone gels from other prosthesis, nor on the gel declared in the manufacturer's dossier. The contact of the gel with biological tissues may be caused by a rupture of the shell or a leak of gel through the intact shell. This could lead to inflammatory reactions in certain patients due to the irritant property of this gel.

- both in vitro genotoxicity tests give negative results,

- the results obtained in vivo on an initial micro-nucleus test were inconclusive, therefore the test was performed again on mice, optimising the experimental conditions in order to get close to the implantation conditions of the prostheses. It was completed by another in vivo test, also performed on mice, the Comet assay. These two additional tests did not reveal any modification of the DNA of mice cells.

Therefore, the results of these tests do not reveal any genotoxic effect of the PIP gel.

These results allow to eliminate the genotoxic risk for PIP gel, explain the occurrence of certain complications such as the inflammatory reactions related to the irritant property of the gel and to draw-up recommendations for women who have or have had PIP implants.

**Also read**

(4) Breast implants pre-filled with silicone manufactured by the company POLY IMPLANT PROTHESE: information/safety recommendations - Letter to health professionals (28/09/2010)

(5) The results of the tests on silicone gel breast implants from the company Poly Implant Prothèse - Information point (28/09/2010)

(6) Results of the complementary tests on the silicone gel breast implants from the company Poly Implant Prothèse - Information point

# 3 - Summary of the vigilance data available in March 2011

## I - Vigilance data that led to the decision of March 29, 2010

The reports of medical device vigilance incidents concerning implantable prostheses, including all manufacturers, have been monitored by the Afssaps for several years according to a deviation analysis method. This method consists in compiling bi-annually all the data concerning incidents observed and comparing them to the data transmitted by the manufacturers, in particular the sales volume, typologies encountered and the expected rate of incidents of each typology in order to identify any abnormal variation in the incident rate for a given manufacturer or a given incident typology.

Thus, the analysis performed by the agency at the end of 2009 on the 2008 data revealed an increase in the rate of incidents, and in particular the rupture rate, on breast prostheses pre-filled with silicone gel manufactured by the Company PIP.

**Table 1 : Cumulative rupture rates of PIP silicone implants calculated from the declaration by non-hospital health professionals and health establishments between 2001 and 2008**

| Declaration of non-hospital health professionals and health establishments | | | | |
|---|---|---|---|---|
| Year of declaration | 2005 | 2006 | 2007 | 2008 |
| Cumulative rupture rate | 0.0297% | 0.0346% | 0.0382% | 0.0651% |

The cumulative rupture rates presented in table 1 were calculated according to the ratio:

$$\text{Cumulate rupture rate} = \frac{\text{cumulative number of rupture reports from establishments or health professionals}}{\text{cumulative number of prostheses sold by the manufacturer}}$$

Table 1 shows a deviation for PIP starting in 2008, during which the cumulative rupture rate doubled regarding to the previous year (0.0382% in 2007 to 0.0651% in 2008). However, this rupture rate, calculated from the vigilance reports of non-hospital health professionals and health establishments, remains the same order of magnitude as that observed with other manufacturers, making the detection of the deviation difficult.

## II - Vigilance data updated since March 30 2010

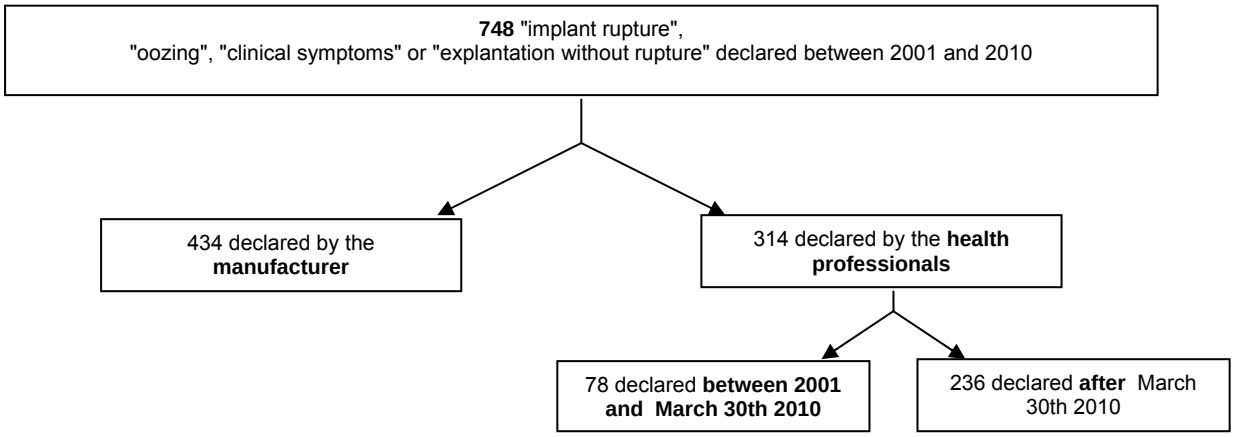
The Afssaps has analysed data concerning PIP silicone implants collected within the medical device vigilance scope, and has updated them since March 30th 2010.

These data came from the incidents declared to the Agency from 2001 to 2010, completed by a survey of the main user establishments and a direct on-site data collection. The objective was to complete and refine the data available in order to estimate the PIP prostheses rupture rate and identify any clinical complications related to the PIP silicone gel.

## 1- Analysis of incident declarations

### 1.1 Methodology

The analysis of incidents concerned 748 incidents, declared by health professionals or the manufacturer, reporting: "implant rupture", "oozing", "clinical symptoms" or "explantation without rupture"




Among the 236 incidents declared by health professionals after the decision of March 2010:
- 83.1% concerned incidents detected in 2010
- 5.9% concerned incidents detected in 2009
- 2.1% concerned incidents detected in 2008
- 1.3% concerned incidents detected in 2007
- 7.6% did not mention the date of the incident

An increase in the number of incidents declared to the Agency was observed after the health policy decision. Health professionals declared 3 times more incidents in 8 months, from March to December 2010, than in 9 years, from January 2001 to March 2010.

### 1.2 Rupture of implants

Among the reports transmitted to the Agency between 2001 and 2010, 528 rupture incidents were declared. Among these, only 402 mentioned the date of implantation, which is essential information for the analysis.

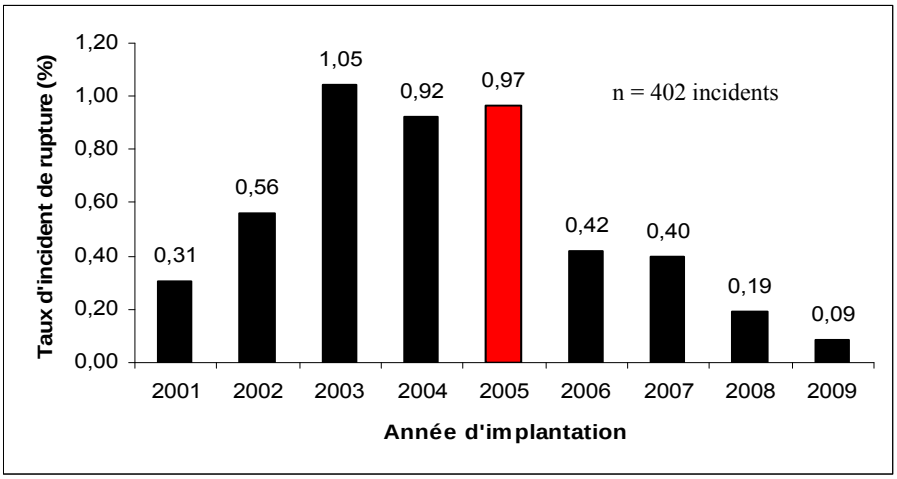



**Figure 1: distribution of rupture incident rates as a function of the implantation year**

The rupture incident rates presented in figure 1 were calculated as follows:

$$\frac{\text{number of prostheses implanted over a year } \lambda \text{ and declared broken to the Afssaps}}{\text{total number of prostheses implanted over the same year } \lambda}$$

This figure shows that the rupture incident rate reaches 1.05% in 2003, and oscillates between 0.92% and 0.97% up to 2005.
Warning: the decrease in the rupture incident rate observed between 2005 and 2009 does not mean that the prostheses implanted over this period presented a lower risk of rupture. It is due to a lack of experience on prostheses implanted after 2005.

On top of that, the analysis of the incident declarations shows that the majority of ruptures occurred within the 5 years after implantation. These results confirm that the lifetime of PIP implants is lower than the expected lifetime of a breast implant.

### 1.3 Oozing

The oozing phenomenon (also called perspiration or transudation) consists in a passage of silicone through the shell of an intact prosthesis.

The analysis of the incidents declared to the Agency reveals 22 cases of oozing, among which 17 cases were discovered in a preventive explantation without clinical or ultrasound sign, confirming that the detection of this phenomenon is difficult.
For 5 cases the oozing was discovered during an explantation performed after the appearance of signs or clinical complications such as pain, adenopathies or delayed wound healing.
The majority (14 cases) of the oozing declared were discovered within the 3 years following the date of implantation. Therefore, it would seem that the perspiration is an early phenomenon.

### 1.4 Clinical complications

The analysis of the incident declarations allows the identification of clinical complications that may be observed with or without implant rupture: siliconomas, grade 3 or 4, inflammatory reactions and effusions, lymphorrhoeas, pain, lymph node disorders and delayed wound healing.

### 1.5 Explantation of implants without rupture

At the end of 2010, 79 explantations without rupture of the implant have been reported to the Afssaps within the vigilance framework. Among these cases of intact prosthesis explantation, several types of cases were identified:

- explantations following the appearance of signs suggestive of an implant rupture (clinical or ultrasound signs), while the implant was in fact intact: this is called "false positives" (n = 16 reports)
- voluntary explantations, at the request of the woman concerned (n = 42 reports)
- preventive explantations of the controlateral prosthesis in case of rupture of one of the two implants (n = 21 reports)

This low number of explantations declared at the end of 2010, is due to the fact that the circular requiring health professionals to report all cases of explantation of PIP silicone prosthesis, even without deterioration of the implant, was issued in October 2010.

## 2 - Analysis of the retrospective survey data

### 2.1 Methodology

A retrospective investigation was carried out among the establishments using the PIP prostheses for plastic or reconstructive breast surgery.

This investigation was performed among the main users and declarants. The compilation of the data requested by the agency from the user centres within a limited time represented an important workload for the establishments, which explains the small number of responses. It should be noted that the patients followed in a given establishment were not necessarily implanted in the same establishment.

### 2.2 Rupture of implants

The investigation confirms the rupture rate ranging between 0.37% to 11.11% (see table 2).

**Table 2 : rupture rate actually observed in women seen by the surgeons who have responded**

| Establishment | Number of women followed | Estimated number of prostheses implanted in the women followed | Number of ruptures confirmed after explantation | Rupture rate |
|---|---|---|---|---|
| Establishment 1 | 98 | 98 | 3 | 3.06% |
| Establishment 2 | 54 | 54 | 6 | 11.11% |
| Establishment 3 | 430 | 817 | 3 | 0.37% |
| Establishment 4 | 169 | 338 | 3 | 0.89% |
| Establishment 5 | 37 | 74 | 7 | 9.46% |
| Establishment 6 | 210 | 399 | 9 | 2.26% |

### 2.3 Oozing, clinical complications and explantations of implants without rupture

The retrospective survey did not allow to obtain additional data concerning the oozing phenomenon and the preventive explantations and did not reveal any new clinical complications.

## 3 Analysis of on site compilation data

### 3.1 Methodology

In order to complete the data available, a complication of data on site, directly from the patient records, was carried out in two major PIP prostheses implantation centres specialised in breast reconstruction.

### 3.2 Rupture of implants

The results concerning PIP silicone implant ruptures compiled on site are presented in table 3.

**Table 3 : Rupture rate actually observed in women followed in the two establishments**

| | PIP prosthesis implantation period | Number of women followed | Estimated number of prostheses implanted in the women followed | Number of ruptures confirmed after explantation | Rupture rate |
|---|---|---|---|---|---|
| Establishment 1 | 2002 - 2010 | 682 | 1023 | 25 | 2.44% |
| Establishment 2 | 2008 - 2010 | 45 | 45 | 0 | 0% |

In the first establishment, user of PIP prostheses from 2002 to 2010, a rupture rate of 2.44% was observed on 1023 prostheses implanted in the women followed. In the second establishment, no implant rupture was observed among the 45 prostheses implanted in the 45 women followed. However, these prostheses have only been implanted since 2008.

### 3.3 Oozing

The results concerning oozing are presented in table 4.

**Table 4 : Oozing rate observed in women followed in the two establishments**

| | PIP prosthesis implantation period | Number of women followed | Estimated number of prostheses implanted in the women followed | Number of oozing observed during explantation | Oozing rate |
|---|---|---|---|---|---|
| Establishment 1 | 2002 - 2010 | 682 | 1023 | 22 | 2.15% |
| Establishment 2 | 2008 - 2010 | 45 | 45 | 5 | 11.1% |

In the first establishment, the perspiration rate was 2.15% out of 1023 prostheses implanted in the women followed. In second establishment, this rate was 11.1% out of 45 prostheses implanted in the women followed.
All the cases of perspiration were observed at 3 years or less post-implantation in the two centres visited, which seems to confirm that this phenomenon occurs early.

It should be noted that in case of implant rupture, this phenomenon is masked by the presence of silicone in the prosthetic casing. Thus, perspiration is only detected during preventive explantations of intact prostheses.

### 3.4 Clinical complications and explantation of implants without rupture

The collection of data on site did not reveal any new clinical complication and did not allow to obtain any additional information concerning preventive explantations without rupture.

## Conclusion on vigilance data

The investigations carried out on the user's sites of PIP breast implants revealed major variation in the rupture rate between centres.

Furthermore, the vigilance data show the emergence of a type of incident rarely described prior to the March 30, 2010 decision: the oozing phenomenon. The analysis of the vigilance data shows that oozing is only observed in case of explantation of intact implants and that it is an early phenomenon, mainly detected within the first 3 years following implantation.

This phenomenon is a source of additional and early exposure to PIP silicone gel and is difficult to detect in a clinical way or with imaging.

# 4 - Follow-up recommendations for women with PIP implants and information on the PIP dossier

On March 30th, 2010 the Afssaps issued an initial series of recommendations concerning the monitoring of the women concerned. These recommendations have been updated regarding the test results and the vigilance data.

To date, regarding these elements and in particular the absence of genotoxic effect observed, the recommendations of the Afssaps are the following:

1. For women with PIP's gel implants, Afssaps recommends:

- A clinical examination and an ultrasound scan every 6 months, targeting for each of these exams, breasts and axillaries lymph node areas.
- That any rupture, suspected rupture or oozing of prosthesis should lead to its explantation, as well as that of the second prosthesis.

In case of rupture or oozing, an accumulation of gel in the axillary lymhph nodes (adenomegaly) may trigger pain and/or inflammation. Even in the absence of clinical sign, the invasion of the lymph nodes may be detected by palpation and/or ultrasound. Their ablation may be considered in case of highly incapacitating symptoms (pain, functional disorder). It must not be systematic in view of the risks of complications that may result ("big arm", sensibility disorders).

Afssaps reminds that contact with the surgeon is an opportunity to discuss a possible explantation without clinical signs of deterioration of the prosthesis: the concerned women will consider the most appropriate attitude according to their personal situation, their feelings, the age of their prostheses and their expectations at the aesthetic level. This choice will take place after evaluation by the surgeon of the individual risk / benefit ratio, based on a preoperative assessment that takes into account medical history, surgical and anaesthetic risks, and the risk of complications inherent in the surgery.

For this purpose, the Afssaps published on its website a decision making assistance guide (7) intended for women with PIP silicone breast implants and surgeons. This guide was written with the collaboration of multi-disciplinary experts, patient associations (8) and the Société française de chirurgie plastique, reconstructrice et esthétique (SOFCPRE) (9). It presents the advantages and disadvantages of the two possible options, i.e. leaving the PIP implants in place or explanting them in a preventive manner.

2. For women who turn to explantation of their PIP's implants, Afssaps doesn't recommend any specific follow-up.

However, if the implant was broken or showed signs of leakage of the gel, these elements must be recorded in the medical file of the patient to be taken into account in any subsequent clinical examination. Indeed, taking into account that gel can built up in the lymph nods over time, even after explantation achieved, any increase in the lymph nodes must be connected to the presence of PIP's gel.

Finally, in case of re implantation of new implants, Afssaps reminds that a yearly clinical follow-up is recommended.

The Afssaps has requested the assistance of several learned societies, organisations and associations to disseminate the recommendations as widely as possible in order to facilitate the procedures of women with PIP implants with different health professionals. Thus, the SFR (société française de radiologie), the SFAR (société française d'anesthésie réanimation), the SFG (société française de gynécologie), patient associations, the National medical board and the SOFCPRE have been informed of the decisions taken by the Agency.

Besides, the SOFCPRE participated in the drafting of documents intended for the general public within the framework of a broader collaboration convention with the Agency.

Since September 2010, the Agency has communicated to the CNAM (health insurance) all the elements of the PIP dossier necessary for the modification of the management of women with PIP implants for aesthetic purposes. The new management procedures are available on the Health insurance website (10).

On the other hand, the Afssaps reminds you that a document (11), updated in April 2011 and covering the answers to the most frequently asked questions about this dossier is available on its website.

**Also read**

(7) PIP breast implants: decision-making assistance guide (06/12/2010)
(8) Link for the Patient associations:
- PPP http://association-ppp.wifeo.com
- MDFPIP http://www.mdfpip.com/
(9) SOFCPRE: http://www.plasticiens.org/
(10) Link for the coverage conditions by the health insurance: http://www.ameli.fr/assures/soins-et-remboursements/combien-serez-vous-rembourse/implants-mammaires.php
(11) Updated Answers-Questions