



Scientific Committee on Health Environmental and Emerging Risks
SCHEER

SCIENTIFIC ADVICE ON
Evaluation of the availability of new scientific information
on the safety of PIP breast implants



The SCHEER adopted this final Scientific Advice
on 28 September 2017

ABSTRACT

Following a request from the European Commission, the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) hereby provides an inventory of new information available on the safety of Poly Implant Prothèse (PIP) silicone breast implants to evaluate whether an update of the 2014 SCENIHR Opinion on the safety of the PIP breast implants (2014 Opinion) is warranted.

In addition to conducting a literature review, a public call for scientific information was launched. The literature review showed that new information is available regarding the possible health effects of PIP breast implants, but this information is rather limited. Also, the public call for information did not result in the submission of scientific papers regarding health effects specific to PIP implants, but rather on breast implants in general. Therefore, on the basis of the new scientific information gathered, the SCHEER concludes that an update of the 2014 Opinion is not warranted.

New scientific information was found relating to the early and increased PIP implant rupture risk, which suggested that the risk was probably due to the low quality of the implant's shell as already reported in 2014 Opinion. Based on new data, the rupture rate of PIP silicone breast implants was calculated to about 23%, which is similar to the 25% - 30% rupture rate indicated in the 2014 Opinion.

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

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SCHEER

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This Scientific Advice has been subject to a commenting period of ten weeks after its initial publication (from 7 April until 15 June 2017). Comments received during this time were considered by the SCHEER.

The comments received were considered to be outside the scope of this advice as they were providing additional information on possible adverse effects of SBI in general.

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1 MANDATE

1.1 BACKGROUND

A. The safety of the PIP silicone breast implants

Over many years, the PIP manufacturer fraudulently made use of industrial silicone instead of the approved medical grade silicone in many of the breast implants produced. Investigations were triggered by an unusually high short-term breast implant rupture rate. The product was thereafter withdrawn from the EU market.

Following this fraud, SCHENIR was requested to provide two scientific Opinions on the safety of the PIP silicone breast implants. The first one, a rapid scientific Opinion, was adopted by SCENIHR on 1 February 2012¹. This Opinion was updated by a second one, adopted on 12 May 2014.²

Given the importance of the matter, the Commission relevant services, DG GROW and DG SANTE, are committed to monitoring the publication of new and valid scientific information and facilitating possible update of the 2014 Opinion on the PIP silicone breast implants in the light of such new scientific data.

Besides its regular consultation of the National Competent Authorities, DG GROW and DG SANTE recognise the need for a formal scientific evaluation of the current availability of new and relevant information.

This need is also highlighted in the remarks of the European Ombudsman's Decision in case 174/2015/FOR on the Commission's alleged failure to investigate conflicts of interests relating to the adoption of a report on the safety of removing PIP breast implants: "*The Commission should continue to evaluate new scientific data relating to the safety of PIP implants.*"³

The investigation into the availability of new scientific data that would warrant an eventual update of the May 2014 Opinion on the safety of the PIP breast implants should take into account all the necessary fields and especially those covered by the previous Opinion, such as the physiochemical properties of PIP implants, their toxicology, the clinical impact and recommendations.

B. Possible association between breast implants in general and anaplastic large cell lymphoma

Anaplastic large cell lymphoma (ALCL) is a very rare type of lymphoma. ALCL is not a cancer of the breast tissue and the prognosis of the disease is generally favourable. A possible association between breast implants and ALCL is under scrutiny in the European Union and at international level by regulators and scientists.

According to an estimation⁴ of the US-Food Drug Administration, in 2011 there were between 100-250 known cases of ALCL in women with breast implants out of an

¹ http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_034.pdf

² http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_043.pdf

³ <http://www.ombudsman.europa.eu/cases/decision.faces/en/61195/html.bookmark>

⁴ <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239995.htm>

estimated number of 5 to 10 million women who have received breast implants worldwide.

The information to date suggests that women with breast implants may have a very low but increased risk of developing ALCL, while the rarity of the disease makes it difficult to establish a definite causal relationship (Center for Devices and Radiological Health U.S. Food and Drug Administration).⁵

Given that this suspected association between breast implants and ALCL appears to be an emerging risk, the SCHEER should determine whether there is enough scientific information available to allow for a full risk assessment of the matter. The existence of information on a specific association with PIP silicone breast implants should also be investigated.

1.2 MEANS OF ACHIEVING THE GOALS

In order to make a thorough collection of all the data on the two aforementioned issues, two actions were considered:

- 1) Holding a public call for data open to all stakeholders, and holding it open long enough to ensure that any information pertaining to the two topics may be submitted.
- 2) Conducting a review of the published scientific literature and of any other source of relevant data available on the two topics.

The relevant scientific information should be retained and should serve as the basis for the SCHEER to reply to the questions described in the terms of reference. Any rejection of acquired information should be justified. The Committee will decide if both topics may be addressed by one call for data and one scientific literature review at the same time or if separate processes need to be organised.

1.3 TERMS OF REFERENCE

Following the assessment of the availability of the scientific information the SCHEER should:

- 1) Indicate whether there is sufficient new scientific information to warrant an update of the May 2014 Opinion on the safety of the PIP breast implants
- 2) Provide a formal Advice on the state of scientific knowledge regarding a possible connection between breast implants and anaplastic large cell lymphoma

⁵ <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239996.htm>

2 CONCLUSIONS

Following the request received from the European Commission, the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) performed a literature review and launched a call for information to gather new scientific information related to the safety of the PIP breast implants, which became available after the publication of the Opinion on the safety of Poly Implant Prothèse (PIP) Silicone Breast Implants - Update of the Opinion of February 2012⁶ (2014 Opinion).

Based on the analysis of the literature review, it is concluded that insufficient new information is available to warrant an update of the 2014 Opinion. New scientific information was found relating to the early and increased PIP implant rupture risk, which suggested that the risk was probably due to the low quality of the implant's shell as already reported in 2014 Opinion. The calculation of the rupture rate based on PIP explants indicates a rupture rate of PIP breast implants of approximately 23%, similar to the 25% - 30% rupture rate presented in the 2014 Opinion.

The call for information did not result in the submission of any scientific data and/or information regarding health effects specific to PIP breast implants. A lot of information was submitted concerning breast implants in general but not focusing specifically on PIP breast implants. This information was considered not relevant for the evaluation of the availability of new scientific data on the safety of PIP breast implants.

In conclusion, the new scientific information gathered, both via the call for information and via the literature review, was considered insufficient and an update of the 2014 Opinion is therefore unwarranted.

3 MINORITY OPINION

None

4 DATA AND METHODOLOGY

4.1 Introduction

This document provides an inventory of the information on the safety of PIP silicone breast implants which became available after the publication of 2014 Opinion, to evaluate whether an update of the 2014 Opinion is warranted.

This Scientific Advice answers question one of the 'Terms of Reference' of the mandate.

The state of scientific knowledge regarding a possible connection between breast implants and anaplastic large cell lymphoma is presented in a separate document.

⁶ http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_043.pdf

4.2 Methodology

New scientific information on the possible adverse effects of PIP breast implants was obtained by two independent methods: a literature search and an open call for information. All submitted information was considered but conclusions were based exclusively on peer-reviewed scientific papers.

The literature search was conducted to retrieve scientific literature available on PIP breast implants. The major search terms, PIP and breast implants were used in combination with additional terms listed below. Papers were selected based on the search terms using PubMed and Find-eR (a tool for searching multiple library resources in one interface which includes the European Commission Library collections, plus millions of online full-text journal articles and eBooks). The publication period of the scientific papers covered was from January 2012 to August 2016.

Literature search using PubMed resulted in 366 entries. Table 1 below shows the key words used and number of papers obtained. Duplicate articles were obtained because the search included more key words.

Table 1- Results from PubMed

Key words including MeSH terms (PubMed) ⁷	No of hits
("Phys Perspect"[Journal] OR "pip"[All Fields]) AND (("silicones"[MeSH Terms] OR "silicones"[All Fields] OR "silicone"[All Fields]) AND ("breast implants"[MeSH Terms] OR ("breast"[All Fields] AND "implants"[All Fields]) OR "breast implants"[All Fields]))	59
(Poly[All Fields] AND Implant[All Fields] AND Prothese[All Fields]) AND implants[All Fields]	51
"PIP" (All Fields) AND ("breast implants"[MeSH Terms] OR ("breast"[All Fields] AND "implants"[All Fields]) OR "breast implants"[All Fields]) AND ("infection"[MeSH Terms] OR "infection"[All Fields])	13
(PIP) breast implant AND cancer	81
(PIP) AND breast implants AND infection	13
(PIP) AND breast implants AND inflammation	12
(PIP) AND breast implants AND rupture	36
(PIP) AND breast implants AND risk assessment	11
(PIP) AND leakage AND breast implants	8
(PIP) AND breast implants AND safety of implants	38
(PIP) AND breast implants AND silicone gel	44

Table 2 below shows the key words used and number of papers obtained using Find-eR, a tool for searching multiple library resources in one interface. It includes the European

⁷ MeSH (Medical Subject Headings) is the NLM controlled vocabulary thesaurus used for indexing articles for PubMed

Commission Library collections, plus online full-text journal articles and eBooks. Duplicate articles were obtained because the search included more key words. Literature search using FIND-eR resulted in 72 entries.

Table 2- Results from FIND-eR

Key words	No of hits
PIP AND Silicone Breast Implants	6
PIP AND Breast implants	9
PIP AND silicone implants	7
PIP and implants	13
PIP AND Cancer	5
(PIP) AND Inflammation	0
PIP AND Rupture	3
PIP AND breast implants	5
PIP and Anaplastic Large Cell Lymphoma	2
(PIP) AND breast implants AND risk assessment	3
(PIP) AND safety of implants	5
Breast implants AND safety of implants	12
(PIP) AND silicone gel	2

In addition, a call for information was launched by the European Commission to invite all interested parties to submit scientific information regarding the safety of PIP breast implants. The call for information was published on 14 June 2016 and closed on 4 September 2016. For on-going studies and research that were not completed by the deadline, the call remained open until 20 November 2016.

Among of all information received, the SCHEER considered only peer-reviewed papers focusing specifically on the safety of PIP breast implants.

5 ASSESSMENT

5.1 Sources of information

5.1.1 Results from the literature review

99 papers were obtained from PubMed and 10 publications from Find-eR. A table was prepared to facilitate the evaluation of the new scientific information collected (both via the literature review and via call for information), containing the following categories:

- Identification number
- Title
- Authors

- Name of the journal
- Year of publication
- Peer review or not
- Concerning PIP: this tag means that the paper contains data and results on clinical studies specifically regarding PIP implants
- Mentioning PIP: this tag means that the paper cites PIP breast implants but not related to the safety assessment of the PIP breast implants
- Type of study design: case report, non-human experimental study, observational study, clinical trial, randomized clinical trial, other=not a clinical study
- Sample size: number of patients included
- Comments made by the evaluators

A compilation of the papers used for the evaluation is presented in Table 3.

Only papers published in peer-reviewed journals describing data and results on clinical studies specifically regarding PIP implants were considered. Commentaries, editorials, and discussions on silicone breast implants (SBI) in general or on the PIP breast implant fraud case were not considered for further evaluation.

The Pubmed search resulted in 99 papers. After the removal of 8 duplicate publications retrieved via Pubmed, a total of 91 papers were included in the compilation of papers to be evaluated.

The search using the Find-eR tool resulted in an additional 10 papers which were not duplicates of those retrieved via Pubmed. The papers obtained consisted mainly of book chapters dealing with various aspects of silicone breast implants and one EU report on Notified Bodies. One paper described an assessment of Notified Bodies in the EU. These papers, although included in the list of papers to be evaluated, did not provide information relating to PIP implants specifically but to various aspects of SBI in general. As book chapters and the Notified Body report are usually not peer reviewed, this information was not considered for further evaluation.

Table 3. Papers evaluated as presented in Annex 1.

Papers dealing with rupture evaluation	39
Papers of reviews SBI and/or PIP fraud	14
Papers dealing with comments/news on PIP fraud	20
Papers dealing with other subjects	27

The evaluation of each paper is presented in Annex 1.

The reviews and studies evaluated did not consistently indicate that PIP implants induced more harm to patients compared to other SBI brands (Moliter *et al.* 2015, Wazir *et al.*, 2015). Therefore, the additional risk of PIP breast implants may be limited to the high rupture rate which is probably due to a low quality of the PIP breast implant shell. Indeed, most studies indicate a higher rupture rate of PIP breast implants when compared to other SBI brands. In one study the prevalence of PIP breast implant

ruptures was comparable to other SBI brands, but with an increase in ruptures over time (Leckenby *et al.*, 2016). Also early adverse events were not different between PIP breast implants and two other SBI brands (Mentor(®) and Allergan(®)) (Fenoll *et al.*, 2015).

In conclusion, the literature review showed that new information is available regarding the possible health effects of PIP breast implants, but this information is rather limited.

5.1.2 Results from the call for information

Five stakeholders submitted information regarding possible health effects of PIP breast implants, accounting for a total of 87 papers. However, only 12 papers are related to PIP breast implants, 6 of which were also included in the literature review mentioned above. The evaluation of the papers provided via the call for information is presented in Annex II. None of these 12 papers contained scientific information related to the health impacts of PIP breast implants on patients. For example, the submitted papers discussed the analytical chemistry of the PIP silicones or shell and some papers discussed the rupture rate of PIP breast implants. Most of the other papers discuss SBI in general or are comments/editorials in journals not containing scientific information on the health aspects of PIP breast implants.

5.1.3 Information submitted during commenting period

A commenting period on the scientific Advices was published on the website of the Scientific Committees from April 7th until June 15th, 2017. Two organisations and one individual (providing in total 10 documents) submitted comments and provided input supposed to be related to the topic of the scientific advice, i.e. the toxicity of PIP silicone breast implants. Each contribution was carefully considered by the SCHEER and submitted papers were evaluated (see Annex III). In general the information did not specifically discuss the toxicity of PIP implants. The SCHEER concluded that the comments were outside the scope of this advice as they were providing additional information on possible adverse effects of SBI in general.

5.2 Rupture rate of PIP breast implants

The probability of rupture for PIP breast implants reported in the 2014 Opinion is around 25-30% at 10 years after implantation. In order to estimate the current PIP breast implant rupture rate, a calculation was made based on the papers obtained in the literature review and also published studies already considered in the 2014 Opinion (Table 4). The rupture rate was determined based on data for 4641 implants and 3461 patients (Table 4). This re-analysis resulted in a rupture rate of about 23% (95% confidence interval 17.5% to 27.9%), which is in the same range as the rupture rate of 25%-30% presented in the 2014 Opinion.

Some studies show that the mean time from PIP implantation to rupture diagnosis and/or explanation was relatively short and generally less than 10 years. This may reflect the consequences of the PIP breast implant fraud case, which prompted regulatory bodies and the plastic surgery society to advise that PIP implants be removed as a preventive

measure rather than only when necessitated by the appearance of clinical symptoms.

Moreover, Swarts *et al.*, 2013 showed a highly variable shell thickness in ruptured PIP implants including shell regions below the minimum thickness specified by the manufacturer.

Table 4. References on rupture rate

Author	Number of patients (S)	Rupture rate PIP implants (%) ^a	Implant time at explantation or rupture diagnosis (mean number of years and range)
Billner et al. 2015	64 (115)	23.48	8.4 (n.a.) ^c
Moschetta et al. 2014	21 (40)	50	≥ 7 (n.a.)
Mennie et al. 2015	192 (384)	21	8.7 (6-15)
Schott et al. 2014	72 (108)	23	5.1 (1-11)
Oulharj et al. 2014	455 (828)	7.73	n.a.
Quaba et al. 2013 ^b	338 (676)	21.3	7.8 (1-13)
Berry et al. 2012 ^b	453	24.85 (range 15.9 – 33.8)	n.a. (6-11)
Berry et al. 2013 (update) ^b	460	30.55 (range 22.7 – 38.4)	n.a. (6-11)
Tropet et al. 2013	217 (434)	8.7	4.6 (n.a.)
Aktouf et al. 2012 ^b	99 (192)	11.9	n.a.
Leckenby et al. 2016	455 (905)	14.25	7.8 (0.12-16.8)
De Lorenzi et al. 2015	360 (443)	18.5	4.8 (n.a.)
Scotto di Santolo et al. 2014	64	36	8 (6-14)
Maijers et al. 2014	107 (214)	21	10 (n.a.)
Khan 2013	65	27.7	7.2 (2-12)
Chummun et al. 2013 ^b	39 (78)	21.8	7 (n.a.)
Maijers et al. 2012 ^b	(224)	24	10 (n.a.)

a) Indicated is the rupture rate as determined in explanted PIP breast implants. If the number of explants was not provided in the paper the percentage indicates patients with the diagnosis of implant rupture.

b) Studies on rupture rate of PIP implants included in 2014 Opinion on PIP breast implants.

c) n.a. not available

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ANNEX I: Evaluation of papers identified through literature search

In this Annex are listed the papers identified through literature review, using Pub-Med and Find-eR and the evaluation made by the SCHEER.



**Literature review
PIP.docx**

ANNEX II Evaluation of papers received during the call for information

In this Annex are listed the papers received via call information which was published on the 14th of June 2016 and closed on September 4th 2016 and the evaluation made by the SCHEER.



Papers received
during the call for info

ANNEX III Evaluation of papers received during the commenting period

In this Annex are listed the papers during the commenting period which was opened from April 7th until June 15th, 2017



Evaluation of the
literature received du