TO: **Department of Health, NHS Medical Directorate**

Document Purpose For Information
Gateway Reference 17744

Poly Implant Prothèse (PIP) breast implants: the final report of the Expert Group

Published: 18 June 2012

We wish to bring to your attention our very grave concerns about the above mentioned document which is being used as the basis of the care, treatment and regulation in Britain and negatively impacting on more than 47,000 women and their families.

We note that at the time of the Final Report:

Keogh's Expert Group has now 'disbanded' even though Keogh acknowledges some vital test data is still pending. (K37 pg15)

Test data concerning "irritancy" (one of three tests on regulated medical implant devices class III (high risk) containing medical grade silicone) were not available. Nor were the data for tests on breast milk. The work to measure the concentration of the siloxanes is also "still in progress".

1. **Test results on breast milk (in mothers with ruptured PIP implants) were not available (K10 pg7)**

According to Keogh's Expert Group report "the PIP batches showed higher levels of low molecular weight cyclic silicones" (K7ii pg6) and goes on:

"In theory it is possible that the lower molecular weight siloxanes could migrate into breast milk; the MHRA have therefore arranged for chemical analysis of a sample of breast milk from a patient with ruptured PIP implants and we will publish the results as soon as they are available. In the meanwhile, in the light of the advice in the SCCP[1] review, we consider that there is no reason to depart from the current MHRA advice."

[1] Scientific Committee on Consumer Products (European Commission)

Current MHRA advice to breast feeding mothers is "There is also no evidence of any harm to breast feeding infants in women who may have experienced ruptures in their PIP implants."[2]

- we note the Scientific Committee on Consumer Products SCCP/0893/05[3] referenced and referred to as the SCCP Review in (K10 pg7) states

"Octamethylcyclotetrasiloxane (D4) is classified as toxic for reproduction category 3."

- we note in Chemical Analysis (K7ii pg 6) "***the PIP batches showed higher levels of low molecular weight cyclic silicones*** (the siloxanes including octamethylcyclotetrasiloxane (D4), decamethylcyclopentasiloxane (D5), and dodecamethylcyclohexasiloxane (D6))"

- we note in (K10 pg7) "10.***Silicone polymers of high molecular weight*** are considered highly unlikely to cross the barrier into breast milk"

We demand immediate and urgent clarification of this unconscionable advice to breast-feeding mothers with ruptured PIP implants as Octamethylcyclotetrasiloxane D4 was at the time of the SCCP review a "substance(s) classified pursuant to Directive 67/548/EEC as carcinogenic, mutagenic or toxic for reproduction, of category 3,"

- we also note evidence from victims in the Australian Senate Community Affairs References Committee May 2012[4] (K reference 11)

4.23 One submitter spoke of the health issues her child experienced since birth which may be attributed to breastfeeding with ruptured PIP breast implants:

My ultrasound report was both implants ruptured with right hand side silicone in lymph nodes. Left one was leaking. I went into panic and shock. My baby was under 10 weeks old and I immediately stopped breastfeeding as I couldn't bare even the thought of feeding him through potentially toxic and unknown substances in my breast. He already had enough health problems
Department of Health and Ageing, *Poly Implant Prothese Breast Implants: Report of the Chief Medical Officer*, April 2012, p. 17.
Name withheld, *Submission 32*, p. 2. Name withheld, *Submission 26*, p. 2.....
My recent baby was born with fluid on his lungs, enlarged lymph nodes and cyst on his adrenal gland. I had a tougher pregnancy with him with a lot of pain on my right side ie pelvis, kidney, abdominal and headaches. He was born at 36.5wks. When he was around 5 wks old I was rushed to emergency in an ambulance again with unexplained right side pain.[21]

- We also note with serious concerns the response from Dr Fleming and the CMO

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[2] http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/Product-specificinformationandadvice-A-F/Breastimplants/Typesofbreastimplants/index.htm

[3] http://ec.europa.eu/health/archive/ph_risk/committees/04_sccp/docs/sccp_o_035.pdf

[4]http://www.aph.gov.au/Parliamentary_Business/Committees/Senate_Committees?url=clac_ctte/implants_2012/report/index.htm

4.24 When questioned about the potential risk of breastfeeding with these implants, Dr Daniel Fleming from the Australasian College of Cosmetic Surgeons provided the following explanation:

The silicone molecules are too large to get into the milk and there is more silicone in supermarket milk than there is in the breast milk of women with silicone breast implants.[22]

4.27 The Chief Medical Officers (CMO) report on PIP breast implants which was published on 7 May 2012[25] was silent on the issue of breastfeeding.

4.28 The Committee understands the deep concern felt by mothers concerning the effect ruptured implants could have on their children through breastfeeding. The committee notes the advice provided by the Therapeutic Goods Administration about breastfeeding children with PIP breast implants, however also noted the limited nature of evidence regarding the impact breastfeeding while having ruptured PIP breast implants.

Recommendation 12
4.29 The committee recommends that the clinical advisory committee established by the Chief Medical Officer should develop advice, based on current evidence regarding breastfeeding and PIP breast implants, as soon as possible, and that this information be included in future Chief Medical Officer reports on this issue.

21 Name withheld, *Submission 13*, p. 1.
22 Dr Daniel Fleming, *Committee Hansard*, 9 May 2012, p. 27.
25 Department of Health and Ageing, answer to question taken on notice, 9 May 2012, received 23 May 2012.

- We also note the Committee's recommendations and concerns over the limited evidence.

2. Tests results for irritancy, were not available (K12 pg7)

-we understand tests for 'irritancy' are negative in medical grade silicone (SC Toxicity Tests pg4)
-we note in the Keogh Report 'irritancy' tests are referred to as 'skin irritation' tests (K11 ii pg7)
-we note PIP implants tested positive in *in vivo* tests at SCENIHR

"However, an in vivo test for irritancy was positive. This indicates the potential for inducing local irritancy (which may manifest as sore and/or enlarged local lymph nodes or sensation in the breast) when the silicone gel is released from the implant. The form that local irritancy might take will depend on the amount released, the duration of exposure and other local conditions. The implications of this positive result in an irritancy test, for women with PIP silicone breast implants are currently uncertain and further investigation is required.[5]"

[5] http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_034.pdf

- We also note British Surgeons published comments and concerns

"I've looked at this in detail and I'm satisfied about this – the gel is an irritant and causes an inflammatory effect...[6]" (PT)

"The infamous Poly Implant Prothèse products and the French company that created them are currently in the middle of a public healthcare scandal. The medical problems that have been reported with the PIP implants include irritation and inflammation after rupturing of the breast implants.[7]"

"This can be a particular problem for patients with PIP implants as the gel used in PIP implants is **irritant to the tissues** as may cause inflammatory lumps typically in the breast itself or in the **lymph nodes in the armpit**. These lumps may need to be removed along with the implants.[8]"

"Once outside the protective shell (in the case of leak/ rupture), the non-medical grade silicone gel filler used by PIP can migrate causing irritation and inflammation of the surrounding breast tissue. Rupture can also result in breast lump formation (siliconomas) and/ or the enlargement of the adjacent lymph glands (under the armpit).[9]"

According to the European Parliament adopted text of 14 June 2012 "**the SCENIHR report requested by the Commission in early January 2012 stresses that there is some concern regarding the possibility of inflammation induced by ruptured or leaking PIP silicone implants;**"[10]

3. **Test results relating to concentrations of siloxanes were not available** (K7.ii pg 6)

> "Work to measure the concentration of the siloxanes is still in progress and will be published as soon as the data are available..." (K7 ii pg6)

4. According to Keogh "**The possible implications for human health have been studied in a 2004 review by the Scientific Committee on Consumer Products**[11] (SCCP) and, in the specific context of PIP breast implants, in recent work by the TGA's expert panel. **The conclusion drawn is that even in the event of a complete rupture of a PIP implant there would be no significant risk to human health**." (K8. pg7)

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[6] **E P L Turton FRCSEd FRCS(genSURG) MD(Hons) Consultant Breast Oncoplastic and Aesthetic Breast Surgeon (PT)**

[7] http://www.cadoganclinic.com/pip-replacement-of-breast-implants/

[8] http://www.staianoplasticsurgery.co.uk/pips.html

[9] http://quaba.co.uk/blog_files/PIP_breast_implants.html

[10] http://www.europarl.europa.eu/sides/getDoc.do?type=TA&language=EN&reference=P7-TA-2012-262

[11] http://ec.europa.eu/health/archive/ph_risk/committees/04_sccp/docs/sccp_o_035.pdf

-The SCCP cited review adopted during the 6th plenary meeting of 13 December 2005 did not reach this conclusion. It said:

"On the basis of provided data, the SCCP is unable to assess the risk to consumers when Octamethylcyclotetrasiloxane (D4) is used in cosmetic products.

Despite the size of the dossier submitted by industry for evaluation, it is unfortunate that the dossier lacked meaningful information/data on actual consumer exposure to D4."[12]

The TGA citation provides an update on the Laboratory testing program as follows[13]: which provides no evidence to support Keogh's assertions concerning risk to health. Published 16 March 2012 accessed 26 July 2012.

TGA laboratory testing program - an update Top of page

The scientific investigation undertaken by the TGA is one piece of a complex risk assessment being undertaken by health authorities in Australia and overseas to determine the health risks associated with having PIP breast implants.

One of the concerns with PIP breast implants has been the use of an unauthorised silicone gel. The French regulatory authority, AFSSAPS, has reported that the authorised and unauthorised silicone gels have different ingredients which can result in differences in the physical and chemical properties of the gel. In particular, AFSSAPS noted that some batches of unauthorised gels contained higher amounts of small silicone molecules (called low molecular weight siloxanes) than the authorised gel.

The TGA is continuing to measure the amounts of these small molecules in different batches of PIP breast implants. The results of the tests carried out so far are summarised in the table below.

Type of siloxane (small silicone molecules)	Quantity in parts per million	
	range	median
D4	0-261	136
D5	0-710	434
D6	0-1005	474

These results are generally consistent with the results obtained by the French authorities. The results of the TGA testing have not shown any relationship between year of manufacture and the presence of these small silicone molecules. Results of further testing will be published when the information becomes available.

5. Actual studies on the known or suspected health effects of D4, D5 and D6?

The Scientific Guidance Panel (SGP) at a Meeting of the California Environmental Contaminant Biomonitoring Program (CECBP) USA reported the known or suspected health effects of D4, D5 and D6, more recently in December 4-5, 2008[14]. They detail the Known or suspected health effects of D4, D5 and D6.

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[12] http://ec.europa.eu/health/archive/ph_risk/committees/04_sccp/docs/sccp_o_035.pdf

[13] http://tga.gov.au/safety/alerts-device-breast-implants-pip-120316.htm#laboratory

[14] http://oehha.ca.gov/multimedia/biomon/pdf/1208cyclosiloxanes.pdf

Known or suspected health effects

D4 animal toxicity studies found changes in organ weights (Burns-Naas et al. 2002, McKim et al. 2001a, He et al. 2003), induction of hepatic drug metabolizing enzymes (McKim et al. 1998), and adverse effects on reproductive health and function, including weak estrogenic effects (Stump et al. 1997 and 1999, He et al. 2003, Quinn et al. 2007a and 2007b, Siddiqui et al. 2007, Meeks et al. 2007; McKim et al. 2001b). D4 exposure has also been associated with the development of benign uterine tumors (adenomas) in rats (Plotzke et al. 2000).

D5 has been shown to cause uterine endometrial adenocarcinomas in female rats (Dow Corning, 2005). D5 also has adverse health effects on the reproductive system, adipose tissue, bile production, and the immune system through its effects on prolactin, and it has the potential to cause adverse effects on the nervous system because of its influence on the neurotransmitter dopamine (OEHHA 2007).

D6 The liver is thought to be the target organ for oral exposures, and potentially for inhalation exposures (Environment Canada 2008). D6 exposure has been associated with liver and thyroid enlargement and reproductive effects (Dow Corning 2006). Model calculations suggest that D6 has the potential to affect aquatic organisms at concentrations close to its water solubility (Environment Canada 2008).

6. Unscientific use of incommensurable data and false analogies with medical grade silicone and fraudulent PIP breast implants.

“despite extensive toxicology testing, no evidence has yet been found that any of the chemical constituents of silicone gel are potentially harmful ...In this respect... PIP silicone gel is no different from the gels used in other implants.” (K27 iii pg12)

- We note that Reuters reported “In 2008, PIP invested 300,000 euros on a new machine to make the implants’ shells, hoping more uniformity would cut leakage, according to Couty. (PIP CEO) Brinon, PIP’s technical director, said Mas came to him in early 2008 and told him to start developing a new gel, PIP 2. Brinon refused, and the task went instead to another worker who had never worked on implants before coming to PIP. The goal, he said, was to create a gel that would not leak so much oil. This was crucial: silicone gel that seeps out may cause irritation and inflammation in women’s bodies.[15]”

7.**ALCL and PIPs are not referenced.**

“despite extensive toxicology testing, no evidence has yet been found that any of the chemical constituents of silicone gel are potentially harmful and no biologically plausible mechanisms have been suggested to link silicone gel with the symptoms described.” (K27 iii pg 12)

[15] http://graphics.thomsonreuters.com/specials/Implants.pdf

"It is worth noting that it was a French report of this very rare cancer that sparked the most recent publicity[16]."

7 December 2011 : TGA received information from AFSSAPS about a case of ALCL associated with a PIP implant and confirming its previous advice to patients. AFSSAPS requested specific information about breast implants and cases of ALCL in Australia[17]

FDA "Is collaborating with the American Society of Plastic Surgeons (ASPS) and other experts in the clinical and scientific community to develop a registry of women with breast implants and anaplastic large cell lymphoma (ALCL) to better understand the nature and possible factors contributing to their association;" (FDA 06/11 pg33)

"Based on all evidence available to us at this time, the FDA believes that women with breast implants may have a very low but increased risk of developing ALCL."[18]

"...ALK-negative anaplastic large-cell lymphoma involving a seroma associated with a breast implant, is an emerging clinicopathologic entity. Anaplastic large-cell lymphoma has been identified in association with breast implants and seroma formation relatively recently.[19]

- We note in the USA, FDA consumer advice January 2011 "After an intensive review of known cases of a rare form of cancer in breast implant recipients, the Food and Drug Administration (FDA) says women with implants may have a very small, but increased risk of developing anaplastic large cell lymphoma, or ALCL.[20]"

8 Neither British nor USA Cancer Data is referenced.

- we note with deep concerns, the news of the death of a 40yr Scottish mother of two Susan Grieve.[21]

9. We dispute the assertion that conclusions reached by European Union's

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[16] http://quaba.co.uk/blog_files/PIP_breast_implants.html

[17] TGA May 2012 ISBN 978-1-74229-645-6

[18] http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm241086.htm

[19] http://www.ncbi.nlm.nih.gov/pubmed/20309431 J Hematop. 2009 Aug 20;2(4):237-44. Rare lymphoid malignancies of the breast: a report of two cases illustrating potential diagnostic pitfalls. Farkash EA, Ferry JA, Harris NL, Hochberg EP, Takvorian RW, Zuckerman DS, Sohani AR.

[20] http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm240985.htm

[21] http://www.dailyrecord.co.uk/news/real-life/2012/07/01/family-fears-healthy-mum-aged-40-died-from-cancer-caused-by-controversial-pip-breast-implants-86908-23903123/

Scientific Committee on Emerging and Newly Identified Health Risks[22] (SCENIHR) and Keogh Expert Group Report are 'similar'. (K5. pg5)

"in general, there is little variation in chemical composition from batch to batch and little difference between PIP and medical grade silicone." (K7 i pg6)

"In the light of the findings from the chemical analysis, that there is little variation in chemical composition between batches of PIP implants made over a period of 5 years, it seems increasingly unlikely that testing of further samples will reveal any cause for concern." (K13 pg8)

"It should be noted that PIP silicone breast implants have been found to vary considerably in composition and, as a result they are likely to vary substantially in performance characteristics. No clear temporal trend of implant problems has been identified for PIP silicone breast implants. Consequently it is very difficult to identify a truly representative PIP implant for testing purposes." (SC Abstract pg4)

Further evidence of varied composition comes from PIP employee police statements and statements from Nusil (only registered supplier of Medical grade silicone in France) confirm no purchases of medical grade silicone were made by PIP between 2003-2005.

10. **The Adopted Texts of 14/06/2012 European Parliament**[23] were published 4 days prior to the publication of the Keogh Report, reference the same SCENIHR documents and **outline a superior standard of care, treatment and regulation for women in Member states**.

11. **We strongly disagree that further tests are unnecessary, in fact we consider such a statement both unscientific and deliberately harmful**.

"we do not believe that a further research study at this stage is likely to yield any useful information on whether, in general, PIP implants are likely to pose a risk to health as compared to other implants." (K28 pg12)

"The FDA[24] activities surrounding silicone gel-filled breast implants focus on three key goals:

- Fostering the collection of data about implant performance;" ...

The European Parliament Adopted Text of 14 June 2012[25], "12. Stresses that the testing procedures and standards for breast implants should be refined to allow a better understanding of the interaction of the shell material with the filling gel and the surrounding body fluids, and of the fatigue and tear resistance of the shell and the total implant;

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[22] http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_034.pdf

[23] http://www.europarl.europa.eu/sides/getDoc.do?type=TA&language=EN&reference=P7-TA-2012-262

[24] http://www.fda.gov/DOWNLOADS/MEDICALDEVICES/PRODUCTSANDMEDICALPROCEDURES/IMPLANTSANDPROSTHETICS/BREASTIMPLANTS/UCM260090.PDF

[25] http://www.europarl.europa.eu/sides/getDoc.do?type=TA&language=EN&reference=P7-TA-2012-262

considers that more proposals should be made for research to develop non-destructive methods of testing of implants;"

The European Commission[26] has specifically asked SCENIHR to:
1. To contribute to the creation of an EU questionnaire to be used for the collection of data on implanted patients;
2. To provide guidance on the testing undertaken by the member States in terms of tests and studies to be performed, test methodologies, uniform data production;
3. To collect, compile and analyse the data collected;
4. To update its scientific opinion on the safety of the PIP silicone breast implants."
5. Deadline: 31 January 2013"

Berry MG and Stanek JJ. authors of The PIP mammary prosthesis: a product recall study[27]. cited in the Keogh report think long term studies are essential. They say "Long-term studies such as this are difficult to undertake ... They are, however, essential from an industry perspective both for the provision of information and supporting audit and professional standing."

"When the FDA approved silicone gel-filled breast implants in the U.S. in 2006, it recognized that there were limited data on rare events and long-term outcomes. In order to better understand the long-term performance of these devices and to monitor for previously unrecognized adverse events, the FDA required the manufacturers to conduct post-approval studies, analyzed silicone gel-filled breast implant Medical Device Reports (MDR) submitted to FDA, performed periodic literature reviews, and evaluated correspondence from researchers, health care providers, patients, and concerned citizens.[28]"

12. **We consider patients' reported symptoms invaluable as opposed to 'unhelpful'.**

"There have been widespread reports of systemic symptoms associated with PIP implants – generalised pain, respiratory problems, anxiety, fatigue – and calls for the Department of Health to collect information to assess the frequency with which such symptoms occur. We have considered this carefully but did not feel that such a data collection would be helpful..." (K27 pg12)

"symptoms described are common in the general population" and ..."the possibility that women with PIP implants might be more likely to report symptoms than a matched sample from the general population;" (K27i pg12)

"The experts said there was no need to commission further research into systemic symptoms reported by women with PIP implants – generalised pain,

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[26] http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_q_031.pdf

[27] http://www.ncbi.nlm.nih.gov/pubmed/22405818

[28] http://www.fda.gov/DOWNLOADS/MEDICALDEVICES/PRODUCTSANDMEDICALPROCEDURES/%20IMPLANTSANDPROSTHETICS/BREASTIMPLANTS/UCM260090.PDF

respiratory problems, anxiety and fatigue. Such symptoms were common to the general population and it would be difficult to establish a sufficiently robust control group with which to make a comparison, they said.[29]"

•"similar symptoms have been ascribed to other breast implants in the past, and a number of very careful epidemiological studies have been carried out" (K27. ii pg12 ref 20)

-We note three of "the very careful epidemiological studies' cited are old: 1998, 2001 and 2004. The fourth and most recent being 2007 by the same principal author as the 2001 study.

"The [Health] Committee was ... very keen to hear about personal experiences of implant surgery from a private provider or the NHS, and how far particular concerns about implants had been addressed."[30] Unfortunately the forum was closed after a month, during which time fewer than 1% of British women had viewed it.

> To accomplish these goals, the FDA:...Actively encourages and facilitates adverse event reporting by the manufacturers, patients, healthcare providers, and health care facilities" (FDA June 2011 pg 33)

> "4.20 The committee acknowledges the common health issues and adverse experiences of Australian women with PIP breast implants, particularly the emotional and financial stress this situation has caused." (TGA4.20 pg50)

"Over the years we have heard from countless women who are saline and silicone breast implant patients and who have suffered from complications, involving both short- and long-term health conditions believed to be related to their implants. Implants rupture and leak. Implants sometimes migrate. Implants often harden and cause capsular contracture. Nearly all will need to be replaced at some point. Reported conditions involve local infections, necrosis, hematoma, connective tissue disorders and immune disorders like fibromyalgia, rheumatoid arthritis, chronic fatigue syndrome, multiple sclerosis, lupus, Sjogren's syndrome and others. National Cancer Institute studies indicate that women who have breast implants are at increased risk of brain cancer, lung cancer, emphysema, pneumonia and suicide. Although research paid for by implant companies disagrees, those findings need to be evaluated by independent researchers. And now we learn that a rare type of immune system cancer, anaplastic large-cell lymphoma (ALCL), is found growing near the capsule of scar tissue around the breast implant. The risk of developing ALCL for women with implants was significantly higher than that found in women without breast implants."

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[29] http://www.guardian.co.uk/world/2012/jun/18/pip-breast-implants

[30] http://forums.parliament.uk/pip-implants/index.php?list,1

Testimony of Terry O'Neill, President, National Organization for Women (**NOW**) Foundation[31] Presented by Jan Erickson, Director, NOW Foundation Programs to the U.S. Food and Drug Administration, General and Plastic Surgery Devices Panel Review of Post-Approval Studies for Silicone Gel-Filled Breast Implants **August 30, 2011**

13. **We strongly contend the report's conclusions and emphatically dispute the validity of 'evidence'** supporting the conclusion, that any amount of caesium, platinum or toluene in the human body carries no risk to human health.

14. **Independent toxicological testing** of **explanted** PIP implants and the response to our FOI request to the MHRA, **indicate levels of several highly toxic chemicals including caesium, platinum, toluene** and D4.

15. "It has been frequently suggested[11] that testing of intact PIP implants should be supplemented by tests on prostheses that have been explanted, for instance after rupture." (K9 pg7)

5.19 The committee notes that there is limited evidence regarding whether poor manufacturing has contributed to the current situation with PIP breast implants. Further, it is unclear whether implants with unauthorised gel have been used in the Australian market which only testing of implants that have been removed will determine. The committee strongly urges the TGA to undertake testing of explanted PIP implants as a matter of priority to inform official advice about PIP manufacturing quality. (SCA[32])

- We believe that no such explanted tests have been undertaken by MHRA

16. **"Silent Ruptures"**

"Doctor Ruth Waters is a consultant plastic surgeon at Queen Elizabeth Hospital in Birmingham. She said: "It's not easy to diagnose a ruptured implant clinically, especially early on."The scans, whether it's ultrasound or MRI, are not 100% fool-proof.[33]"

"It is also important to realise that these implants not only have a high rupture rate but they also have a high bleed rate. This is where silicone gel can gradually pass through the casing into the area around the implant. This can occur with other implants, though Allergan, for example, have three layers to the casing of their implants which includes a special barrier layer to reduce this. For the PIP implants, any silicone bleed is significant as the gel on the inside is an irritant so it can cause a problem. So a patient might not necessarily have a rupture but still might not be safe." (PT)

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[31] http://www.now.org/

[32] http://www.aph.gov.au/Parliamentary_Business/Committees/Senate_Committees?url=clac_ctte/implants_2012/report/index.htm

[33] http://www.bbc.co.uk/newsbeat/18906863

17. The TGA have analysed the “milky fluid” described by some surgeons on explantation of PIP implants[12] and concluded that it consisted essentially of a suspension of silicones in water, rather than the product of some inflammatory reaction. (K9 pg7)

- **We expect to see test results on ‘milky fluid’ but understand the MHRA has written to doctors advising them no further data is required.**
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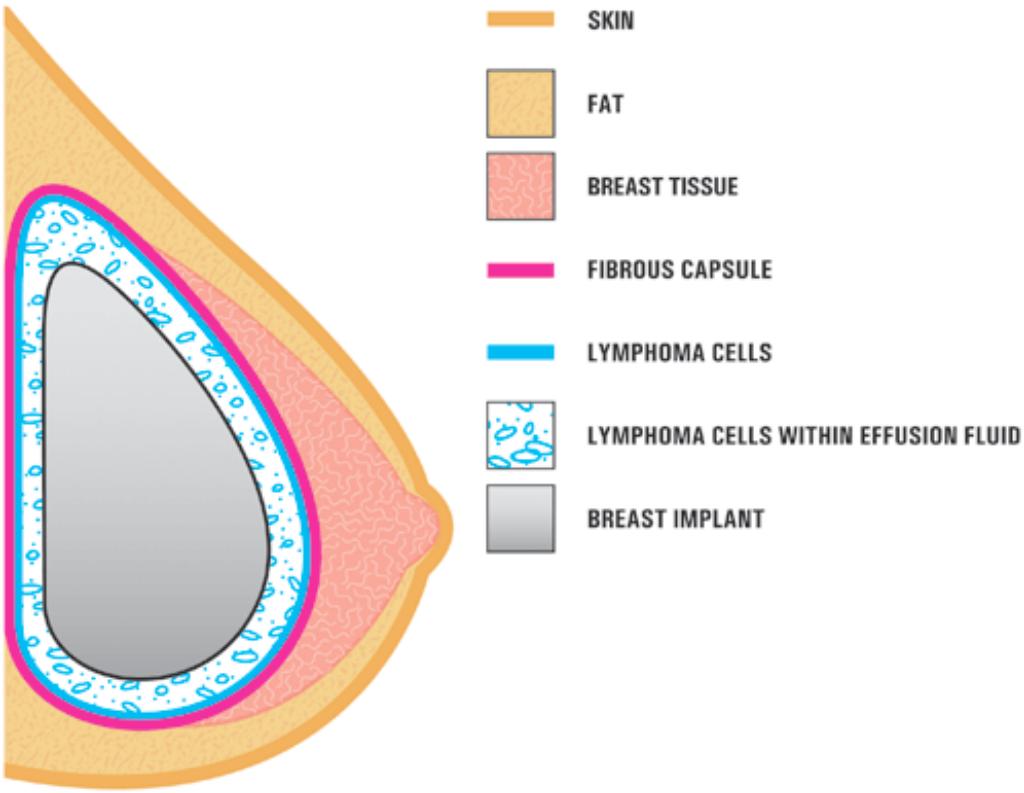
- **Video explant showing “milky fluid” http://youtu.be/BWK86Y5wMqU**

Where in the breast has ALCL been found in women with breast implants?[34]
A5. In the case studies reported in the literature, the ALCL was found near the breast implant, contained within the fibrous scar capsule, and not in the breast tissue itself. The illustration below shows the location of the ALCL in these reports. In most cases, the ALCL cells were found in the effusion fluid (seroma) surrounding the implant or contained within the fibrous scar capsule. [Modified from Thompson et al, 2010]



Anaplastic Large Cell Lymphoma (ALCL) In Women with Breast Implants: Preliminary FDA Findings and Analyses, January 2011.[35]

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[34] http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM241046.pdf

[35] http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239996.htm

18. For simplicity, we have concentrated on two main composite outcomes: (K16 pg 8)

- We note and are outraged by the assertion stated on (K2) **What we knew at the time of our interim report (January 2012):** that "One test carried out by the French authorities suggested that PIP implants could cause skin irritation in rabbits."

  - A press statement by Afssaps[36] (now the Agence Nationale de Sécurité du Medicament, ANSM) dated 8 December 2011 reported the death of a woman with PIP implants:

"On 5 December 2011, Afssaps [6] received a report of a case of breast cancer (adenocarcinoma) in a patient who had been using PIP implants for several years. Just a few days ago, another case of cancer (anaplastic, large-cell lymphoma) caused the death of a woman using PIP implants.

Given the documented aberrations occurring with PIP implants, which led to their withdrawal from the market in March 2010, this new information justifies upgrading the recommendations issued by Afssaps"[37]

- An article published on 22 June 2012 by LaDépêche[38] reports the "ANSM has identified 48 Cases of Breast Cancer in women with PIP implants, 3 more since the end of March".

19."the failure rate of 1.2% at 5 years and 3.1% at 10 years found in our retrospective study (para 17) is a substantial under-estimate due to incomplete follow-up without imaging, perhaps by a factor of 5-10" (K25 i pg 11)

"Some of the rates from certain clinics were implausible." (PT)

20. The urgent case for prophylactic explantation[39]

Leading British Plastic Surgeon disputes government report clearing PIP dangers
"I think the report is premature. The effects of any substance can take many years to evaluate. Besides which we know that these implants will self destruct so are we seriously suggesting that the GP and the tertiary specialist will be able to change the likely outcome with a verbal reassurance? I would personally not take much comfort in a suggestion to wait and see if the breast changes in shape or for some associated symptoms before seeking removal. Once again it is a masterful brew of scientific reasoning without the addition a pinch of common-sense or humanity".[40]

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[36] AFSSAPS, now the Agence Nationale de Sécurité du Medicament, ANSM

[37] http://ansm.sante.fr/var/ansm_site/storage/original/application/88298749fac7d46f85a1a0828348fda5.pdf

[38] http://www.ladepeche.fr/article/2012/06/06/1371081-implants-mammaires-pip-2252-ruptures-de-prothese-constatees.html

[39] http://www.jprasurg.com/article/S1748-6815(11)00161-6

[40] www.drkirwan.com Professor Laurence Kirwan MD

"(Government) advice is that the **PIP implants are safe to leave** if there are no signs of rupture, but you should be monitored annually by your GP or your private healthcare provider.

The **advice from the professional associations is different**. The British Association of Aesthetic Plastic Surgeons (**BAAPS**), the British Association of Plastic Reconstructive and Aesthetic Surgeons (**BAPRAS**), the International Society of Aesthetic Plastic Surgeons (**ISAPS**) and the Association of Breast Surgeons (**ABS**) all feel that **PIP implants should be removed**. Their view is that the implants are not fit for purpose and should not be left in. This view is shared by the governments of France, Germany, Venezuela and the Czech Republic.[41]"

"PIP implants were first used (amongst other implants) at the Murrayfield Hospital in the year 2000. During 2005-2006, a number of cases of unexpected PIP implant ruptures were seen. These were reported to the manufacturing company, its UK distributor as well as the Medical Devices Agency, the then UK regulator. The company did not accept responsibility and its analysis report blamed the implanting surgeons. This prompted a decision to stop using PIP implants at the Murrayfield Hospital in early 2007, three years before the implants were banned by the French authorities[42]."

According to Dr. Dirk Richter (Germany), Chair of ISAPS' Patient Safety Committee, "**as there are no studies yet available to prove the safety of industrial grade silicone in the human body, ISAPS supports the French and German authorities' recommendations and encourages all women with TiBREEZE, PIP or Rofil breast implants produced after 2001, to check with a specialized plastic surgeon to discuss removal of the implants.[43]"**

• All patients should be able to have an assessment by a surgeon regardless of whether they have symptoms
• If a patient requests removal - they should expect to get this, regardless of the presence of any symptoms
Scanning alone is not a reliable enough tool for detecting failure rates in breast implants[44]

"We remain of the opinion that it's not the rupture rate that is the issue but the substandard quality of the implant, and reiterate that all PIPs should be removed as

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[41] http://www.staianoplasticsurgery.co.uk/pips.html

[42] http://quaba.co.uk/blog_files/PIP_breast_implants.html

[43] http://www.isaps.org/press-releases-removal-tibreeze-breast-implants.html

[44] http://www.bapras.org.uk/news.asp?id=966

a precaution - as a number of patients still present with inflammatory response despite not experiencing rupture"[45]

"last month, the independent expert group that has been investigating the subject, led by the NHS medical director Professor Sir Bruce Keogh, decided that there is not enough evidence to recommend routine removal of PIP breast implants. One man who would beg to disagree is Adrian Richards, a consultant plastic surgeon who has removed 100 pairs of PIP implants in the past 12 weeks. What he found wasn't pleasant. 'Essentially, 18 per cent of these women have ruptured implants. I know that these figures may be skewed because the women who are coming to me suspect they have problems, but of the remainder, 75 per cent have had a "gel bleed" from the implants. The manufacturer skimped on the quality of the shell, as well as on the contents. Because PIP used a cheap silicone, it reacts with the body creating a sort of pus, which we've never seen before"[46]

"Even without any clinical signs of rupture, these implants should be removed or exchanged to avoid further health risks." ISAPS[47]

In a letter from Mr Adrian Richards MBBS, MSc, FRCS (Plast).

"not enough has been done to prove that PIP'S are safe and we do not know what health issues they may cause in the long term.

What I do know is:

- I have personally removed PIP implants from 210 women in the last 7 months
- 44 of these patients had ruptured implants on one or both sides
- The majority of the intact implants had significant gel bleeds
- The implant ruptures were more severe and extensive than in any other implant I have ever seen
- In the cases where the implants were ruptured I noted 10-100mls of creamy fluid lying within the capsule and in most cases inside the implant mixed with the silicone gel

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[45] http://www.telegraph.co.uk/health/healthnews/9209114/Faulty-PIP-breast-implants-more-likely-to-rupture-than-previously-thought.htmlConsultant

[46] http://www.standard.co.uk/lifestyle/esmagazine/the-men-who-rebuild-breasts-7665530.html

[47] http://www.isaps.org/

- I have not seen the fluid before associated with other types of implants
- As far as I am aware this fluid has not been fully tested and no one has explained why ruptured PIPS should cause the fluid when other implants do not appear to
- In my opinion it is likely that this fluid is in some way be related to the nature of the silicone contained within the PIP implants because:
    - It only occurs if the implant is ruptured- its' presence can in fact alert the surgeon to a very small rupture that they may not have otherwise noticed
    - In my experience it does not occur with other ruptured implants
    - I think it is likely that the fluid is related to the non-medical grade silicone used in PIP's
- In every one of the 44 patients with ruptured there was there was a significant inflammatory response to the implant in the capsule
- A significant number of our patients have mentioned that they have been non-specifically unwell for some years before PIP removal and felt better immediately they had the implants removed.

I totally agree with you that we need long-term studies on the safety of PIP implants. We know that they have a higher rupture rate than other implants. What we do not know is the medical implications of the contents of their gel in the long term. In my experience the gel within PIP implants does not appear to be behaving in same inert fashion as with other implants."

21. We consider the Keogh report inept, cavalier and a disgrace to British Medical Standards, British Scientists and Physicians as well as an act of grievous harm to Women in Britain.

22. We believe the public sector equality duty in s149 of the Equality Act 2010 has been breached and women are subject to a special disadvantage as a result of the advice and the policies adopted by the British Government Regulator MHRA, the Department of Health and the British Government.

What British surgeons say:

"Dr Kirwan has little but scorn for the way the government has responded. 'For some reason, the government decided that this was a moral failing on the part of the physicians using implants - which is non sequitur, as the NHS had used them, too - and they had been freely and legally available. It is very sad our government is so reluctant to take the blame. We depend on the government for analysing and certifying many things that are sold and if we can't depend on it for this it is a serious failing. Even if it was an honest

mistake, it was a mistake and should be put right. This is a health crisis and the government is pussyfooting around with select committees to justify a conclusion that it has already reached.' To him, the issue is very simple. 'If it's industrial silicone, and you don't know what the potential risks are, it has to come out.'"[48] 20.04.2012 ES Magazine

"I have also had concerns with what I have found in some patients: I was removing PIP implants from a patient recently. On the one side, where she had reported swelling and redness, the gel had diffused into multiple holes in the breast tissue itself which had then sealed. After removing the implant I had to puncture each hole individually and the gel oozed out. It was painstaking to clean the breast fully. The other breast had looked completely normal after removing the implant except for right at the very top of the breast where there was a shiny membrane. After dividing this I tracked a tunnel that the gel had formed, up under her collar bone and into the base of her neck. This was an eye opener for me and illustrates the very different behaviour of this silicone gel compared to medical-grade breast implant gel. It also emphasises the importance of a meticulous search for the gel at the time of surgery, from within the breast cavity, where there has been any silicone bleed or rupture. [49]" (PT)

"Breast surgeon Taimur Shoaib, who speaks for the British Association of Aesthetic Plastic Surgeons (BAAPS) in Scotland, said he believed the clinics which fitted the implants had a responsibility to remove and replace them...
He said he was concerned about the lack of sympathy for the victims of the PIP scandal...
...Shoaib, who works at the Nuffield Hospital, said he never used PIP implants himself because of reservations about the company involved. "I didn't put any PIP implants in because they had a bad reputation. The MHRA banned a previous one of their implants in 2001."
He said there was not enough evidence to say the implants were safe.
"This [silicone] is a material which has not been passed for human use. No one really knows what the risks are. There is also a lot of speculation that what has been used in these implants may not just be silicone but may have other components.[50]" (TS)

"What I think is crucial here is that the UK government is basing their advice on incomplete evidence. Take the rupture rate; the UK government's data suggests it is approximately one per cent whereas the French regulatory agency reported it to be closer to ten per cent. The reported rate will likely be low in the UK because until now there has been no requirement for a surgeon to report if they have removed ruptured PIP implants. The pre-existing National Breast Implant register was funded by the Department of Health, but they pulled the plug on it in 2006. So I feel that you have to consider the highest known rupture rates as being a possibility as the very low ones are more likely to be as a result of a lack

[48] http://www.standard.co.uk/lifestyle/esmagazine/the-men-who-rebuild-breasts-7665530.html

[49] http://www.treatmentadviser.com/before-after-pictures/pip-implants

[50] http://www.scotsman.com/business/personal-finance/shock-over-lack-of-sympathy-for-victims-of-pip-ops-1-2412556

of reporting rather than any other reason. Some of the rates from certain clinics were implausible.[51]" (PT)

"The British Association of Aesthetic Plastic Surgeons (BAAPS) said the report highlighted the need for all implant providers to remove the devices – even if there were no symptoms of rupture.

Fazel Fatah, the president of BAAPS, who was part of the expert group, said: "Despite rigorous testing showing no long-term danger to human health from the individual chemicals in the gel, the fact remains that PIPs are significantly more likely to rupture and leak and, therefore, cause physical reactions in an unacceptable proportion of the patients … It will come as no surprise to the many women affected that PIPs have been officially confirmed as defective – this has also been our long-held view, and that the choice of removal should be offered to them by their provider regardless of rupture or symptoms[52]."

Among the Surgical Experts Quoted in this Document

Mr E Philip L Turton FRCSEd FRCS(genSURG) MD(Hons) "studied at the Leeds University School of Medicine and qualified with 3 distinctions and 3 honours. After completing house officer training at St James's University Teaching Hospital he immediately went on to a full surgical training programme. He was awarded the Fellowship to the Royal College of Surgeons in 1996. He spent a two year period performing research and wrote a thesis which led to the award of a higher degree, MD(Hons), as Doctor of Medicine with a commendation. He spent a period in the United States in 1999 on a Traveling Fellowship and visited leading centers: Stanford University Medical Center, California ; University of Colorado, Denver, Colorado; Cleveland Clinic Foundation,Cleveland,Ohio."[53]

Awf Quaba is one of the UK's leading aesthetic **plastic surgeons**. His main practice is based at the Spire Murrayfield Hospital in **Edinburgh** (Scotland) and he also consults at the Edinburgh Clinic.[54]

Laurence Kirwan MD, FRCS, FACS, is a recognised international leader in Aesthetic Plastic Surgery. Professor Kirwan has clinics in Harley Street, London and in New York and Connecticut, USA. He specialises in Aesthetic Plastic Surgery of the face, breast and body.[55]

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[51] http://www.treatmentadviser.com/before-after-pictures/pip-implants

[52] http://www.guardian.co.uk/world/2012/jun/18/pip-breast-implants

[53] http://www.cosmeticbreastsurgeon.co.uk/About.htm

[54] http://quaba.co.uk/

[55] http://www.drkirwan.com/

Fazel Fatah has been a Consultant Plastic surgeon since 1991 when he was appointed at the West Midlands Regional Plastic Surgery Centre. He undertook comprehensive general plastic surgery training in different accredited centres in London, Birmingham and Oxford and was granted the Certificate of Higher Surgical Training in Plastic Surgery by the Royal College of Surgeons.[56]

Adrian Richards MBBS, MSC, FRCS(PLAST)
Mr Richards has specialised in plastic surgery for the last 12 years and in the last 6 years has concentrated on cosmetic surgery. He is one of the few Plastic Surgeons in the UK who specialises in facial plastic surgery – particularly face lift procedures.

Mr Richards has full registration with the General Medical Council No. 3286812 and is a member of both the British Association of Plastic and Reconstructive Surgeons (BAPRAS), the British Association of Aesthetic Plastic Surgeons (BAAPS) and the International Society of Aesthetic Plastic Surgery (ISAPS)[57]

What the press says:

Private hospital told doctors to delay NHS work to boost profits[58]

Letter reveals shocking order to make patients wait months for operations – even if there was no waiting list

'A Department of Health spokesperson said: "Minimum waiting times that do not take account of healthcare needs of patients are unacceptable. Decisions on treatments, including suitability for surgery, should be made by clinicians based on what is best for the patient. This applies regardless of whether a hospital is run by the NHS or the independent sector.'[59]

"In December, 2011, the French regulatory authorities advised women, based on their assessment of the evidence, to consider removal of their PIP implants. The MHRA responded on the same day (Dec 23) by disagreeing with their French counterparts. The MHRA argued that it did "not believe that the associated risks of surgery from breast implant removal can be justified without further evidence". This judgment was hasty, cavalier, and completely counter to ongoing concerns about PIP implants. Bruce Keogh did his best to offer collegial support to the MHRA. He wrote that he agreed that there was "no specific safety concern" and that there was "no clear evidence at present that patients with a PIP implant are at greater risk of harm than those with other implants". But his recommendation that women should have free removal of their implants (if they

[56] http://www.fazelfatah.co.uk/

[57] http://www.adrianrichards.com/about.html

[58] http://www.independent.co.uk/life-style/health-and-families/health-news/private-hospital-told-doctors-to-delay-nhs-work-to-boost-profits-7962582.html

[59] http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm063871.htm

are concerned) effectively overturned not only the MHRA's advice but also that of the Chief Medical Officer (also released on Dec 23). The government had told women who had received PIP implants "not [to] be unduly worried". But that view was quite literally incredible given that women had received implants containing an industrial-grade silicone gel that was not approved for human use. Women should certainly be worried that regulatory procedures in place in the EU and UK have failed them so spectacularly."[60]

As women directly affected by fraudulent PIP breast implants:

We gratefully acknowledge the efforts of British and Overseas Medical Associations, Experts and Surgeons to draw the Government's attention to the failures, omissions and inaccuracies of the Keogh Expert Group Report.

and **WE URGENTLY DEMAND**

- Recognition of International Health Crisis
- Recognition of the significant physical, mental and emotional impact on those affected.
- Urgent Removal and approved replacement (free of charge) of ALL fraudulent PIP, Rofil, Tibreeze and M-implants[61]
- Urgent MRI scan detection / Senior Consultation
- Advice/ help lines available for concerned women
- Urgent help for women who are unable to access their original providers
- European Regulators (TÜV, ANSM and MHRA) held responsible for failures.
- Service providers prosecuted for criminally negligent failures where applicable.
- Urgent Regulatory measures in line with European Commission recommendations
- Immediate implementation of European Parliamentary Standards of care
- Immediate implementation advertising regulations
- Urgent care, treatment, regular on-going monitoring and after-care of all affected women and children.
- No mammograms for women with implants.
- Minimum age 22
- Immediate Reporting patients, doctors, clinics, GPs, healthcare professionals
- Implant Register and passports with immediate effect
- Outline completely new treatment and care protocols
- Ongoing testing and reporting

ADDITIONAL DOCUMENTS: annexed

1. Independent (British) Toxicological tests on explanted PIP implants
2. MHRA Toxicological Tests (2011)

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[60] The Lancet, Volume 379, Issue 9811, Page 106, 14 January 2012 Richard Horton. doi: 10.1016/S0140-6736(12)60032-4

[61] http://www.isaps.org/press-releases-faulty-pip-rofil-medro-breast-implants.html

Additional Web Based Evidence

We draw to your attention video evidence from International Medical Experts, available on youtube and posted to our web page http://pipactioncampaign.org/Add_material.html

NOTE: Dr Grant Stevens and Dr Charles Randquist were both keynote speakers at the Australasian Society of Aesthetic Plastic Surgery (ASAPS) 35th Annual Conference Darwin 3-7 July 2012.

These experts disagree with the findings of the Expert Group Final Report

Dr Grant Stevens (USA) : CNN News 18 June 2012
http://youtu.be/oGqeBX_J3iU

Dr. Grant Stevens outlines his concerns about PIP implants.

Grant Stevens, M.D., FACS, a board certified plastic surgeon and founder of Marina Plastic Surgery Associates is an international keynote speaker at the 35th annual Australasian Society of Aesthetic Plastic Surgery Conference.

Mr Adrian Richards (UK) 18 May 2012
http://youtu.be/NX4N4dOvfOE

Plastic Surgeon Mr Adrian Richards of Aurora Clinics talks us through removal and replacement of a set of ruptured PIP implants.

Mr. Adrian Richards MBBS, MSc, FRCS (Plast.) **Plastic & Cosmetic Surgeon**

Mr Richards was voted 'Home Counties Leading Plastic Surgeon' by The Daily Mail and 'Leading Breast Surgeon UK by The Independent on Sunday.

Mr. Richards qualified as a Doctor in 1988 and for the last 12 years has specialised in plastic surgery. He has full registration with the General Medical Council No. 3286812 and is a Member of both the British Association of Plastic and Reconsructive Surgeons (BAPRAS) and the British Association of Aesthetic Plastic Surgeons (BAAPS), the leading British professional bodies for plastic surgery and reconstructive surgery.

Dr Charles Randquist (Sweden) 20 July 2012
http://youtu.be/DrYXimX4Inw

World renowned plastic surgeon, Dr. Charles Randquist, of Victoriakliniken, Sweden, gives his view on the final report from the UK expert group, regarding PIP-implants. Speech given at the 35th Annual ASAPS Conference in Darwin, Australia, July 2012

FDA Update on the Safety of Silicone Gel-Filled Breast Implants June 2011
Center for Devices and Radiological Health U.S. Food and Drug Administration

"Reproduction and Lactation Problems In the *Core Study*, Allergan reported 45 post-implant reproduction problems in 44 patients over 10 years; most of the problems were spontaneous abortions, miscarriages or infertility. Most of the problems occurred in the primary augmentation and revision augmentation groups. In Allergan's primary reconstruction group, there was one report of a planned abortion to treat a medical problem and one report of no menses. There were no reports of post-implant reproduction problems among women who received the implants for revision reconstruction.
In Allergan's primary and revision augmentation groups, there were 30 post-implant problems with lactation reported in 24 patients, predominantly inadequate milk production. No post- implant lactation problems were reported among women who received the implants for reconstruction or revision reconstruction.
In the *Core Study*, Mentor reported 153 patients with pregnancies over 8 years. Twenty-three of these patients reported miscarriages, and one patient reported a stillborn delivery. Seventy patients reported attempting to breastfeed and of these, 13 reported lactation difficulties and nine reported an inadequate milk supply.[62]

"D4 is a representative low-molecular weight constituent of silicone gel that is soluble enough in biological fluids to migrate from the implant and into surrounding tissues."[63] *Physiologically based pharmacokinetic modeling of the disposition of octamethylcyclotetrasiloxane (D4) migration from implants in humans*. J Long Term Eff Med Implants. 2008;18(2):133-44.

"This investigation of human tissues by a combination of element-specific and species-specific analytical techniques clearly demonstrates for the first time that platinum and siloxanes leak from prostheses and accumulate in their surrounding tissues."[64] *Determination of siloxanes, silicon, and platinum in tissues of women with silicone gel-filled implants.* Anal Bioanal Chem. 2003 Feb;375(3):356-62. Epub 2003 Jan 28.

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[62] http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/UCM260090.pdf

[63] http://www.ncbi.nlm.nih.gov/pubmed/19968622

[64] http://www.ncbi.nlm.nih.gov/pubmed/12589499

Ethyl acetate

_II. Carcinogenicity Assessment for Lifetime Exposure
Substance Name — Ethyl acetate
CASRN — 141-78-6
This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.[65] *Environmental Protection Agency USA*

Dichloromethane

Decision 455/2009/EC of the European Parliament and of the Council amending Council Directive 76/769/EEC as regards restrictions on the marketing and use of dichloromethane
Government department lead
HSE
Main provisions
The decision concerns:

1. A ban on the placing on the market of dichloromethane (DCM)-based paint strippers for use by the general public after 6 December 2011.
2. A ban on the placing on the market of DCM-based paint strippers for use by professionals after 6 December 2011.
3. A ban on the use of DCM-based paint strippers by professionals after 6 June 2012 with the option for Member States to permit continued use subject to certain conditions.
4. Additional safety measures for the use of CM-based paint strippers in industrial installations.
5. Improved labelling of DCM-based paint strippers.

Latest developments
The Decision was adopted by the Parliament and the Council on 6 May 2009 and was published in the Official Journal of the European Union on 3 June 2009. It has now become a Commission Regulation formally amending REACH (Commission Regulation (EU) No. 276/2010).
Next steps
HSE is in discussion with the manufacturers of DCM, with the formulators of DCM-based paint strippers and with users concerning the scope of derogation for professional users and the proof of competence required. There are plans to amend the REACH Enforcement Regulations in order to put the derogation on a statutory footing.
The placing on the market of DCM-based paint strippers for supply to the general public or professionals is due to cease 2 years and 6 months after the Decision enters into force. Use of these products by professionals is due to cease 6 months later, although Member State authorities can derogate from this restriction allowing, subject to conditions, continued supply to, and use by competent professional users in their territories.66 Health and Safety Executive (UK)

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[65] http://www.epa.gov/iris/subst/0157.htm

[66] http://www.hse.gov.uk/aboutus/europe/euronews/dossiers/dichloromethane.htm

Health Hazard Information

Acute Effects:

- The major effect from acute inhalation exposure to chloroform in humans is central nervous system depression. At very high levels (40,000 ppm), chloroform exposure may result in death, with concentrations in the range of 1,500 to 30,000 ppm producing anesthesia, and lower concentrations (<1,500 ppm) resulting in dizziness, headache, tiredness, and other effects. (1,2)
- Effects noted in humans exposed to chloroform via anesthesia include changes in respiratory rate, cardiac effects, gastrointestinal effects, such as nausea and vomiting, and effects on the liver and kidney. Chloroform is not currently used as a surgical anesthetic. (1,2)
- In humans, a fatal oral dose of chloroform may be as low as 10 mL (14.8 g), with death due to respiratory or cardiac arrest. (1,2)
- Tests involving acute exposure of animals have shown chloroform to have low acute toxicity from inhalation exposure and moderate acute toxicity from oral exposure. (3)

Chronic Effects (Noncancer):

- Chronic exposure to chloroform by inhalation in humans is associated with effects on the liver, including hepatitis and jaundice, and central nervous system effects, such as depression and irritability. Inhalation exposures of animals have also resulted in effects on the kidney. (1,2)
- Chronic oral exposure to chloroform in humans has resulted in effects on the blood, liver, and kidney. (1,2)
- EPA has not established a Reference Concentration (RfC) for chloroform. (4)
- The California Environmental Protection Agency (CalEPA) has established a chronic reference exposure level of 0.3 milligrams per cubic meter (mg/m^3) for chloroform based on exposures resulting in kidney and liver effects in rats. The CalEPA reference exposure level is a concentration at or below which adverse health effects are not likely to occur. It is not a direct estimator of risk, but rather a reference point to gauge the potential effects. At lifetime exposures increasingly greater than the reference exposure level, the potential for adverse health effects increases. (5)
- ATSDR has established an acute inhalation minimal risk level (MRL) of 0.5 mg/m^3 (0.1 ppm) based on exposures resulting in liver effects in mice, an intermediate inhalation MRL of 0.2 mg/m^3 (0.05 ppm) based on worker exposures resulting in liver effects in humans, and a chronic inhalation MRL of 0.1 mg/m^3 (0.02 ppm) also based on liver effects in humans. The MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of

adverse noncancer health effects over a specified duration of exposure. (1)

- The Reference Dose (RfD) for chloroform is 0.01 milligrams per kilogram per day (mg/kg/d) based on exposures resulting in fatty cyst formation in the livers of dogs. The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious noncancer effects during a lifetime. (4)
- EPA has medium to low confidence in the RfD due to: medium confidence in the critical study on which the RfD was based because only two treatment doses were used, and a no-observed-effect level (NOEL) was not determined; and medium to low confidence in the database because several studies support the choice of a lowest-observed-adverse-effect level (LOAEL), but a NOEL was not found. (4)

Reproductive/Developmental Effects:

- Little information is available on the reproductive or developmental effects of chloroform in humans, via any route of exposure. A possible association between certain birth outcomes (e.g., low birth weight, cleft palate) and consumption of contaminated drinking water was reported. However, because multiple contaminants were present, the role of chloroform is unclear. (1)
- Animal studies have demonstrated developmental effects, such as decreased fetal body weight, fetal resorptions, and malformations in the offspring of animals exposed to chloroform via inhalation. (1)
- Reproductive effects, such as decreased conception rates, decreased ability to maintain pregnancy, and an increase in the percentage of abnormal sperm were observed in animals exposed to chloroform through inhalation. (1)
- Animal studies have noted decreased fetal weight, increased fetal resorptions, but no evidence of birth defects, in animals orally exposed to chloroform. (1)

Cancer Risk:

- No information is available regarding cancer in humans or animals after inhalation exposure to chloroform. (1)
- Epidemiologic studies suggest an association between cancer of the large intestine, rectum, and/or bladder and the constituents of chlorinated drinking water, including chloroform. However, there are no epidemiologic studies of water containing only chloroform. (1)
- Chloroform has been shown to be carcinogenic in animals after oral exposure, resulting in an increase in kidney and liver tumors. (1)
- EPA considers chloroform to be a probable human carcinogen and has ranked it in EPA's Group B2. (4)
- EPA has determined that although chloroform is likely to be carcinogenic to humans by all routes of exposure under high-exposure conditions that lead to cell death and regrowth in susceptible tissues, chloroform is not likely to cause cancer in humans by any route of exposure under

exposure conditions that do not cause cell death and regrowth. Therefore, EPA has not derived either an oral carcinogenic potency slope or an inhalation unit risk for chloroform[67].

Toluene[68]

Health Hazard Information

Acute Effects:

- The CNS is the primary target organ for toluene toxicity in both humans and animals for acute and chronic exposures. CNS dysfunction (which is often reversible) and narcosis have been frequently observed in humans acutely exposed to low or moderate levels of toluene by inhalation; symptoms include fatigue, sleepiness, headaches, and nausea. CNS depression and death have occurred at higher levels of exposure. (1)
- Cardiac arrhythmia has also been reported in humans acutely exposed to toluene. (1)
- Following the ingestion of toluene a person died from a severe depression of the CNS. Constriction and necrosis of myocardial fibers, swollen liver, congestion and hemorrhage of the lungs, and tubular kidney necrosis were also reported. (1)
- Acute exposure of animals to toluene has been reported to affect the CNS as well as to decrease resistance to respiratory infection. (1)
- Acute animal tests in rats and mice have demonstrated toluene to have low acute toxicity by inhalation or oral exposure. (1)

Chronic Effects (Noncancer):

- CNS depression has been reported to occur in chronic abusers exposed to high levels of toluene. Symptoms include drowsiness, ataxia, tremors, cerebral atrophy, nystagmus (involuntary eye movements), and impaired speech, hearing, and vision. Neurobehavioral effects have been observed in occupationally exposed workers. (1,2)
- Effects on the CNS have also been observed in studies of animals chronically exposed by inhalation. (1,2)
- Chronic inhalation exposure of humans to toluene causes irritation of the upper respiratory tract and eyes, sore throat, dizziness, headache, and difficulty with sleep. (1,2)
- Inflammation and degeneration of the nasal and respiratory epithelium and pulmonary lesions have been observed in rats and mice chronically exposed to high levels of toluene by inhalation. (1)
- Mild effects on the kidneys and liver have been reported in solvent abusers chronically exposed to toluene vapor. However, these studies are confounded by probable exposure to multiple solvents. (1,2)

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[67] http://www.epa.gov/ttn/atw/hlthef/chlorofo.html

[68] http://www.epa.gov/ttn/atw/hlthef/toluene.html

- Slight adverse effects on the liver, kidneys, and lung and high-frequency hearing loss have been reported in some chronic inhalation studies of rodents. (1)
- The Reference Concentration (RfC) for toluene is 5 milligrams per cubic meter (5 mg/m3) based on neurological effects in humans. The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious noncancer effects during a lifetime. It is not a direct estimator of risk but rather a reference point to gauge the potential effects. At exposures increasingly greater than the RfC, the potential for adverse health effects increases. Lifetime exposure above the RfC does not imply that an adverse health effect would necessarily occur. (2)
- EPA has high confidence in the RfC, the studies on which the RfC was based, and in the overall toluene database. There are many high quality chronic human studies available including a subset of studies presenting a cluster of NOAELs for neurological effects below reported LOAELs for all available endpoints. In addition, there are numerous supportive animal studies including those showing reproductive and developmental effects at doses higher than that identified as the point of departure. (2)
- The Reference Dose (RfD) for toluene is 0.08 milligrams per kilogram body weight per day (0.08 mg/kg/d) based on increased kidney weight in rats. (2)
- EPA has medium confidence in the study on which the RfD was based because it was considered an adequate gavage study of subchronic duration. The confidence in the database is also medium because of a lack of chronic oral data, and a lack of adequate data on endpoints of potential concern for toluene including neurotoxicity . For these reasons, there is medium confidence in the RfD. (2)

Reproductive/Developmental Effects:

- CNS dysfunction, attention deficits, minor craniofacial and limb anomalies, and developmental delay were observed in the children of pregnant women exposed to toluene or to mixed solvents during solvent abuse. Growth retardation and dysmorphism were reported in infants of another study. However, these studies were confounded by exposure to multiple chemicals. (1,2)
- Children born to toluene abusers have exhibited temporary renal tubular acidosis. (1)
- Paternal exposure (in which the mothers had no occupational exposure to toluene but the fathers did) increased the odds ratio for spontaneous abortions; however, these observations cannot be clearly ascribed to toluene because of the small number of cases evaluated and the large number of confounding variables. An increased incidence of spontaneous abortions was also reported among occupationally exposed women. However, these studies are not conclusive due to many confounding variables. (1)

- Several inhalation studies have shown toluene to be a developmental toxicant, but not a reproductive toxicant, in rodents. (1)

Cancer Risk:

- Available studies in workers have reported limited or no evidence of the carcinogenic potential of toluene. Similarly, the few available epidemiological studies have failed to demonstrate increased risk of cancer due to inhalation exposure to toluene. However, these studies were limited due to the size of the study population and lack of historical monitoring data. (1)
- Chronic inhalation exposure of rats did not produce an increased incidence of treatment-related neoplastic lesions. (1,2)
- Under the *Guidelines for Carcinogen Risk Assessments* (US. EPA, 2005), the EPA considers that *there is inadequate information to assess the carcinogenic potential of toluene*. (2)

"Toluene may have local as well as systemic harmful effects. It may cause irritation of the eyes, respiratory tract, and skin. Repeated or prolonged contact with the liquid may cause removal of natural lipids from the skin resulting in dry, fissured dermatitis. Low-level, chronic exposure as well as acute exposure to toluene may result in central nervous system depression and decreased memory (1). Symptoms include headache, dizziness, fatigue, muscular weakness, drowsiness, and incoordination with staggering gait, skin paresthesia, collapse, and coma"[69]. *Human Toxic Chemical Exposure - Toluene Pacific Toxicology Laboratories*

n-heptane

Documentation for Immediately Dangerous To Life or Health Concentrations (IDLHs) n-Heptane[70] Centers for Disease Control and Prevention 1600 Clifton Rd. Atlanta, GA 30333, USA

Footnote references contained in quoted text can be accessed from original documents footnoted in this document.

[69] http://www.pactox.com/library/article.php?articleID=21

[70] http://www.cdc.gov/niosh/idlh/142825.HTML

Latest News from ANSM 27/07/2112

GOOGLE TRANSLATED: “The number of ruptured Poly Implant Prosthesis (PIP) is increasing, with 290 additional cases in June 2012, indicates the ANSM.

According to data from the National Security Agency of Medicines and Health Products (ANSM), reported Friday, July 27, 3500 near breaks PIP prostheses were observed in late June. In total, over 2,800 women are concerned.

In addition to the implant ruptures, the carriers of PIP prostheses have also been many inflammatory reactions. A total of 2701 reactions of this type have been reported in late June.

Recommended by the Department of Health, the explants preventive currently affecting more than 7,500 women with breast implants PIP.

The ANSM estimated 30,000 number of French women with PIP breast implants.”[71]
27.07.2012, 17h47 (accessed 29/07/2012 01h30)

Additional Data Collected

- We note “Allergan reported 45 post-implant reproduction problems in 44 patients over 10 years”[72]

- **We initiated collecting simple data from British Women with PIP implants.** In less than twenty four hours we collected Health Surveys from 44 women and attach the summary here.

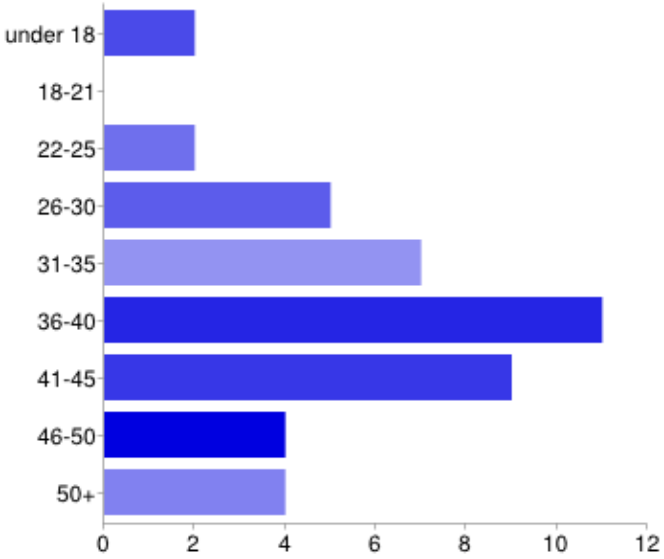
[71] http://www.leparisien.fr/laparisienne/sante/implants-pip-pres-de-300-ruptures-supplementaires-en-juin-27-07-2012-2105459.php

[72] http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/UCM260090.pdf

44 responses

Summary See complete responses

1. How old are you?

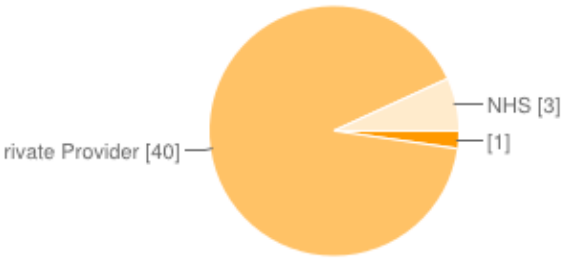


under 18	**2**	5%
18-21	**0**	0%
22-25	**2**	5%
26-30	**5**	11%
31-35	**7**	16%
36-40	**11**	25%
41-45	**9**	20%
46-50	**4**	9%
50+	**4**	9%

2. What year did you have your PIP implants?

2002 2002 2006 2005 2008 2006 2006 2006 harley medical group 2009 2009 2006 2005 &2004 2009 2007 2009 2005 2008 2005 2008 2008 2008 2004 2009 2004 2006 2005 2008 2003 2008 2008 2008 2006 2009 2003 2004 2004 2005 2008 2005 2000 2004 2001

3. Where did your original surgery take place?

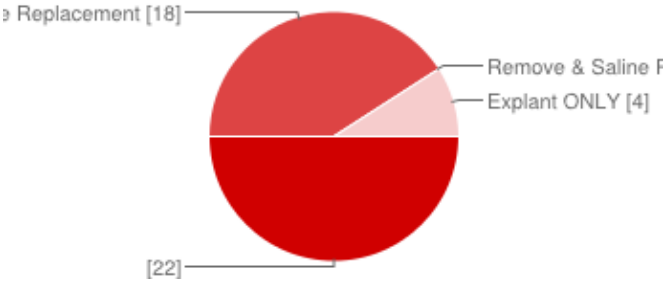


	1	2%
Private Provider	**40**	91%
NHS	**3**	7%

4. Details of your Clinic or Hospital

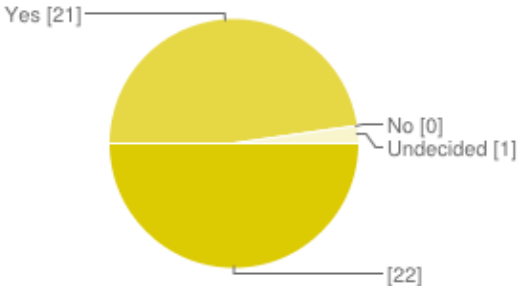
St George's Hospital, London SW17 St George's Hospital, London Durham Bodylooks.. Bmi hospital Manchester surgicare, palatine road, manchester birkdale clinic liverpool HARLEY MEDICAL GROUP leeds lifestyle manchester hospital(surgery) mr sleiter Harley medical group, op at highgate Hos Harley Medical Group London highgate hospital london Harley medical group, Sheffield . Harley Medical Group Highgate Hospital Highgate London Transform highgate hospital London Surgicare, Manchester Life style Hospital birkdale clinic.. crosby, liverpool The Harley medical group - Leeds clinic. Op done by Bernard Sleiter ...

5. Have you had PIP implants removed & replaced?



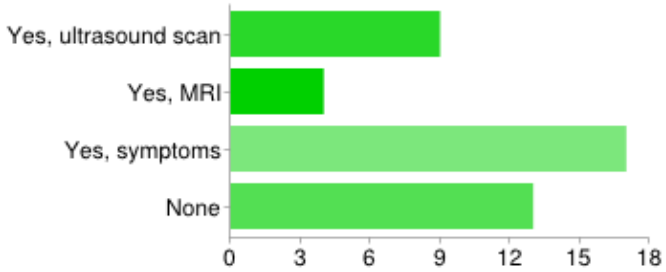
	22	50%
Remove & Silicone Replacement	**18**	41%
Remove & Saline Replacement	**0**	0%
Explant ONLY	**4**	9%

6. If NOT, do you want them removed?



	22	50%
Yes	**21**	48%
No	**0**	0%
Undecided	**1**	2%

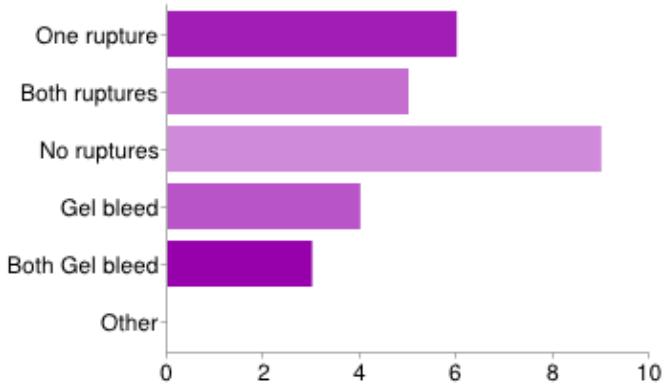
7. Any indication of gel bleed or rupture before surgery?



Yes, ultrasound scan	**9**	24%
Yes, MRI	**4**	11%
Yes, symptoms	**17**	46%
None	**13**	35%

People may select more than one checkbox, so percentages may add up to more than 100%.

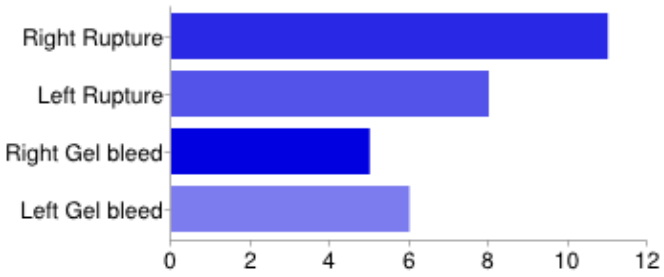
8. Gel bleeds or ruptures discovered on removal?



One rupture	**6**	25%
Both ruptures	**5**	21%
No ruptures	**9**	38%
Gel bleed	**4**	17%
Both Gel bleed	**3**	13%
Other	**0**	0%

People may select more than one checkbox, so percentages may add up to more than 100%.

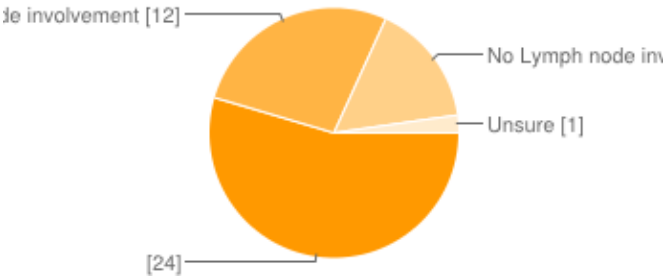
9. If you answered YES, which implants were ruptures/bleeds?



Right Rupture	**11**	69%
Left Rupture	**8**	50%
Right Gel bleed	**5**	31%
Left Gel bleed	**6**	38%

People may select more than one checkbox, so percentages may add up to more than 100%.

10. If your implants bled or ruptured, were your lymph nodes involved?



	24	55%
Yes Lymph node involvement	**12**	27%
No Lymph node involvement	**7**	16%
Unsure	**1**	2%

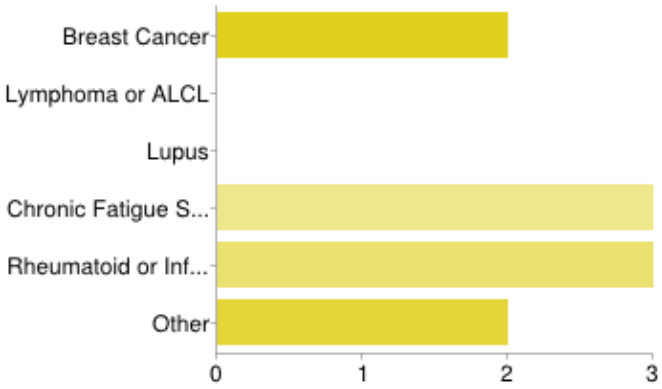
11. Your Symptoms

Blurred vision	**17**	43%
Difficulties tolerating bright or fluorescent lights	**13**	33%
Dry and/or itchy eyes	**18**	45%
Headaches/ Migraines	**26**	65%
Poor concentration	**30**	75%
Memory loss	**24**	60%
Cognitive loss (difficulty finding the right words)	**22**	55%
Depression	**22**	55%
Suicidal thoughts	**9**	23%
Anxiety	**30**	75%
Mood swings	**28**	70%
Anaemia	**8**	20%
Bleeding gums	**14**	35%
Tinnitus (ringing in your ears)	**11**	28%
Pulsatile Tinnitus (hearing your own pulse)	**5**	13%
Shortness of breath	**16**	40%
Stiffness or pain in joints	**29**	73%
Muscle seizures, cramps or spasms	**16**	40%
Muscle weakness	**18**	45%
Previously undiagnosed asthma	**0**	0%
Dry mouth	**17**	43%
Dry skin	**21**	53%
Skin rashes	**16**	40%
Hypersensitivity of skin (can feel like sunburn)	**10**	25%
Tingling or numbness in hands	**23**	57%
Swollen joints	**10**	25%
Excessive sweating	**20**	50%
Night sweats	**23**	57%
Extreme tiredness or fatigue	**36**	90%

Increased bleeding and painful menstrual periods	**11**	28%
Unexplained absence of menstrual periods	**2**	5%
Bladder problems	**12**	30%
Pain in kidneys	**8**	20%
Bowel Problems	**14**	35%
Pain in your breasts	**24**	60%
Itching, tingling or loss of sensation in your breasts	**17**	43%
Swelling or lumps in your breasts	**15**	38%
Swelling or lumps in your armpits	**10**	25%
Hair thinning or hair loss	**19**	48%
Loss or reduction in sex drive	**20**	50%
Unexplained lumps and bumps	**9**	23%
Other	**15**	38%

People may select more than one checkbox, so percentages may add up to more than 100%.

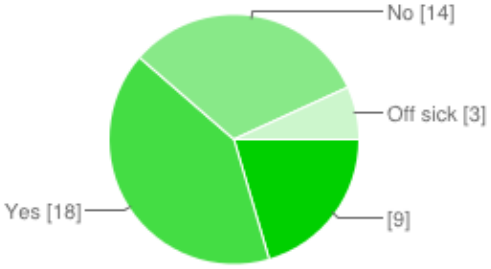
15. Diagnosed Illnesses



Breast Cancer	**2**	25%
Lymphoma or ALCL	**0**	0%
Lupus	**0**	0%
Chronic Fatigue Syndrome	**3**	38%
Rheumatoid or Inflammatory Arthritis	**3**	38%
Other	**2**	25%

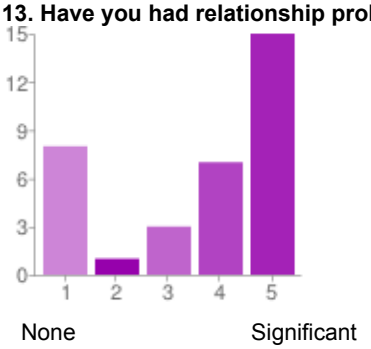
People may select more than one checkbox, so percentages may add up to more than 100%.

12. Have you taken time off work as a result of these symptoms?



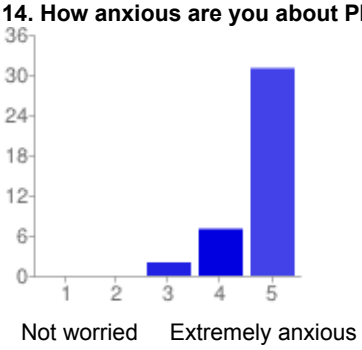
	9	20%
Yes	**18**	41%
No	**14**	32%
Off sick	**3**	7%

13. Have you had relationship problems as a result of symptoms ?



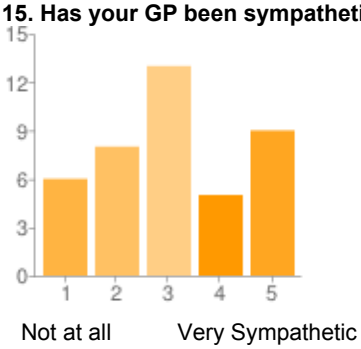
1 -	None	**8**	18%
2		**1**	2%
3		**3**	7%
4		**7**	16%
5 -	Significant	**15**	34%

14. How anxious are you about PIP implants?



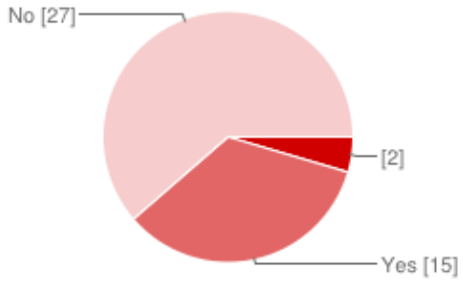
1 -	Not worried	**0**	0%
2		**0**	0%
3		**2**	5%
4		**7**	16%
5 -	Extremely anxious	**31**	70%

15. Has your GP been sympathetic?



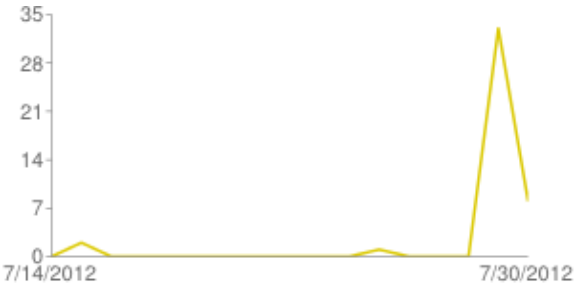
1 -	Not at all	**6**	14%
2		**8**	18%
3		**13**	30%
4		**5**	11%
5 -	Very Sympathetic	**9**	20%

16. Have you delayed seeing your GP to discuss your health issues?



	2	5%
Yes	**15**	34%
No	**27**	61%

Number of daily responses


35
28
21
14
7
0
7/14/2012
7/30/2012

Agenda1

Data Summary

Client: PIP Program
Sample Number(s): 113/002-01 to 113/002-03
Project Number: 113/002
Date of Analysis: 23May12

Results – Headspace GC Analysis of PIP Implants

Samples received were split into outer and inner layers and analysed by Head-Space Gas Chromatography using Agenda1 Test Method GC018 v3, in duplicate using a large and small sample size. The mean results of volatile organic compounds (VOCs) in parts per million (ppm) are reported in this data summary.

Client Sample ID	Client Batch ID	Agenda1 Sample ID
PIP Implant - Stephanie Harris	PIP350CC04505091	113/002-01
PIP Implant - Gail Coxon	L-065	113/002-02
PIP Implant - Grace Charlton	4704	113/002-03

Name of VOCs	113/002-01 Outer Layer	113/002-01 Inner Layer
Ethanol	0.73	0.44
Acetone	1.76	0.08
Ethyl Acetate	0.99	0
Cyclohexanone	0.14	0.17

Name of VOCs	113/002-02 Outer Layer	113/002-02 Inner Layer
Ethanol	0.20	0
Acetone	1.67	0.89
Isopropanol	0.02	0
Ethyl Acetate	1.06	0.08
Butyl Acetate	0.33	0.07
Cyclohexanone	0.09	0.07
1-Butanol	0.53	0
Toluene	0.03	0

Name of VOCs	113/002-03 Outer Layer	113/002-03 Inner Layer
Ethanol	0.22	0.02
Isopropanol	0.18	0.03
Ethyl Acetate	1.68	0
Butyl Acetate	0.12	0
Cyclohexanone	0.40	0.44
Toluene	0.02	0.08
Methanol	0	0.02

Agenda1

Data Summary

Client: PIP Program
Sample Number(s): 113/002-01 to 113/002-03
Project Number: 113/002
Date of Analysis: 23May12

Trace levels of known solvents were found ranging from 0.02ppm to less than 2 ppm. Some extra peaks were also observed, but these were not identifiable by the method, as the standard used was not a comprehensive list of the VOCs available. The results given below are quoted as % peak area of the total peaks found in the samples analysed.

113/002-01		113/002-01	
Outer Layer Sample		**Inner Layer Sample**	
Unknowns Retention time	Unknowns Peak Area %	Unknowns Retention time	Unknowns Peak Area %
36.36	0.05	-	-
40.63	0.15	-	-
-	-	45.27	1.61
46.98	0.18	46.99	0.23
-	-	47.37	2.46
47.42	7.07	47.43	7.97
47.51	36.46	47.51	32.73
51.41	50.98	51.41	52.50

113/002-02		113/002-02	
Outer Layer Sample		**Inner Layer Sample**	
Unknowns Retention time	Unknowns Peak Area %	Unknowns Retention time	Unknowns Peak Area %
46.97	0.01	-	-
46.99	0.65	46.99	2.04
47.21	0.01	-	-
47.44	4.35	47.44	5.60
47.52	21.12	47.51	32.58
51.43	68.79	51.42	44.31

113/002-03		113/002-03	
Outer Layer Sample		**Inner Layer Sample**	
Unknowns Retention time	Unknowns Peak Area %	Unknowns Retention time	Unknowns Peak Area %
10.91	0.50	10.88	0.22
40.63	0.63	40.62	0.62
-	-	45.28	0.52
46.99	0.16	47.00	0.18
47.51	56.0	47.51	57.93
51.42	40.6	51.42	39.45

Data Summary

Client:	PIP Program
Sample Number(s):	113/002-01 to 113/002-03
Project Number:	113/002
Date of Analysis:	23May12

Authorisation

Author: Ayoob Patel (Scientist) — 31May12 (Date)

Approver: Eleanor Hurst (Senior Scientist) — 31May12 (Date)

Final Report

Study Title	Reverse mutation in five histidine-requiring strains of *Salmonella typhimurium*
Test Article	PIP silicone gel breast implant
Study Director	[redacted]
Sponsor	Medicines and Healthcare products Regulatory Agency Biosciences & Implants, Device Technology & Safety Market Towers 1 Nine Elms Lane London SW8 5NQ
Study Monitor	[redacted]
Test Facility	Covance Laboratories Ltd Otley Road, Harrogate North Yorkshire HG3 1PY, ENGLAND
Covance Client Identifier	1008167
Covance Study Number	8232272
MHRA PO Number	3964
Report Issued	March 2011
Page Number	1 of 70

COVANCE
THE DEVELOPMENT SERVICES COMPANY

STUDY DIRECTOR AUTHENTICATION AND GLP COMPLIANCE STATEMENT

PIP silicone gel breast implant: Reverse mutation in five histidine-requiring strains of *Salmonella typhimurium*

I, the undersigned, hereby declare that the work was performed under my supervision and that the findings provide a true and accurate record of the results obtained.

The study was performed in accordance with the agreed protocol and with Covance Laboratories Limited Standard Operating Procedures, unless otherwise stated, and the study objectives were achieved.

The study was conducted in compliance with the United Kingdom Good Laboratory Practice Regulations 1999, Statutory Instrument No. 3106 as amended by the Good Laboratory Practice (Codification Amendments Etc.) Regulations 2004 and the OECD Principles on Good Laboratory Practice (revised 1997, issued January 1998) ENV/MC/CHEM (98) 17.

16 March 2011
Date

QUALITY ASSURANCE STATEMENT

PIP silicone gel breast implant: Reverse mutation in five histidine-requiring strains of *Salmonella typhimurium*

This study has been reviewed by the Quality Assurance Unit of Covance Laboratories Ltd. and the report accurately reflects the raw data. The following inspections were conducted and findings reported to the Study Director (SD) and associated management.

Critical procedures, which are performed routinely in an operational area, may be audited as part of a "process" inspection programme. This can be in addition to phases scheduled on an individual study basis. Selected process inspections conducted and considered applicable to this study are included below.

In addition to the inspection programmes detailed below, a facility inspection programme is also operated. Details of this programme, which covers all areas of the facility annually (at a minimum), are set out in standard operating procedures.

Inspection Dates		Phase	Date Reported to SD and SD Management
From	To		
26 Jul 2010	26 Jul 2010	Protocol Review	26 Jul 2010
02 Aug 2010	02 Aug 2010	Protocol Amendment Review	02 Aug 2010
17 Sep 2010	21 Sep 2010	Draft Report and Data Review	21 Sep 2010
16 Mar 2011	16 Mar 2011	Final Report Review	16 Mar 2011

Process

Inspection Dates		Phase	Date Reported to SD and SD Management
From	To		
07 Jul 2010	07 Jul 2010	Dose Preparation	07 Jul 2010
15 Jul 2010	15 Jul 2010	Test Article Dilutions	15 Jul 2010
15 Jul 2010	15 Jul 2010	Cell line checks	15 Jul 2010
15 Jul 2010	15 Jul 2010	Treatment	15 Jul 2010
15 Jul 2010	15 Jul 2010	S9 Quality Control Checks	15 Jul 2010
16 Jul 2010	16 Jul 2010	Historical Control Ranges	16 Jul 2010
03 Aug 2010	03 Aug 2010	Cell line checks	04 Aug 2010
13 Aug 2010	13 Aug 2010	Treatment	13 Aug 2010
16 Aug 2010	16 Aug 2010	Dose Preparation	16 Aug 2010

[redacted]

16/03/11
Date

REVIEWING SCIENTIST'S STATEMENT

PIP silicone gel breast implant: Reverse mutation in five histidine-requiring strains of *Salmonella typhimurium*

I, the undersigned, hereby declare that I have reviewed this report in conjunction with the Study Director and that the interpretation and presentation of the data in the report are consistent with the results obtained.

[redacted]

RESPONSIBLE PERSONNEL

PIP silicone gel breast implant: Reverse mutation in five histidine-requiring strains of *Salmonella typhimurium*

The following personnel were responsible for key elements of the study:

Study Director
Laboratory Supervisor
Study Monitor [1]

[redacted]

[1] Located at Medicines and Healthcare products Regulatory Agency, London.

ARCHIVE STATEMENT

PIP silicone gel breast implant: Reverse mutation in five histidine-requiring strains of *Salmonella typhimurium*

All primary data, or authenticated copies thereof, specimens and the final report will be retained in the Covance Laboratories Limited archives for one year after issue of the final report. A copy of the electronic data will also be retained. At the end of the specified archive period the Sponsor will be contacted to determine whether the data should be returned, retained or destroyed on their behalf. Sponsors will be notified of the financial implications of each of these options at that time.

CONTENTS

SUMMARY

Samples of PIP silicone gel breast implants were assayed for mutation in five histidine-requiring strains (TA98, TA100, TA1535, TA1537 and TA102) of *Salmonella typhimurium*, both in the absence and in the presence of metabolic activation by an Aroclor 1254-induced rat liver post-mitochondrial fraction (S-9), in two separate experiments.

Each sample of the test article PIP silicone gel breast implant consists of an insoluble outer shell surrounding an insoluble silicone gel. As the test article was therefore insoluble in all commonly used vehicles, extracts of the test article were prepared according to the principles of ISO Guideline 10993, Part 3, 2003 and Part 12, 2007 ([5], [6]). The test article was extracted at 200 mg/mL for 72 hours at 37°C, with shaking, in one organic vehicle (dimethyl sulphoxide, DMSO) and one aqueous vehicle (water). In order to obtain maximum achievable test article treatment levels, the highest volume of each vehicle extract that the assay system will tolerate was used, namely 0.5 mL/plate for water extracts and 0.1 mL/plate for DMSO extracts.

An initial toxicity Range-Finder Experiment was carried out in the absence and in the presence of S-9 in strain TA100 only, using final concentrations of a DMSO extract of PIP silicone gel breast implant at 6.4, 32, 160, 800, 4000 and 20000 µg/plate (equivalent), and final concentrations of a water extract of PIP silicone gel breast implant at 32, 160, 800, 4000, 20000 and 100000 µg/plate (equivalent), plus negative (blank extraction vehicle) and positive controls. Following these treatments, no evidence of toxicity was observed. These data were considered to be acceptable for mutation assessment and are presented in this report as the TA100 mutagenicity data for Experiment 1.

Experiment 1 treatments of the remaining tester strains with water and DMSO extracts of PIP silicone gel breast implant were performed in the absence and in the presence of S-9. The concentrations employed for the Range-Finder Experiment treatments were retained for Experiment 1. Following these treatments, there was again no evidence of toxicity observed.

Experiment 2 treatments of all the tester strains were performed in the absence and in the presence of S-9. The maximum test concentrations of 20000 µg/plate (equivalent) for the DMSO extract or 100000 µg/plate (equivalent) for the water extract were retained for all strains. Narrowed concentration intervals were employed covering the ranges 625 - 20000 µg/plate (equivalent) (DMSO extract) or 3125 - 100000 µg/plate

(equivalent) (water extract), in order to examine more closely those concentrations of both water and DMSO extracts of PIP silicone gel breast implant approaching the maximum test concentrations, and considered therefore most likely to provide evidence of any mutagenic activity. In addition, all treatments in the presence of S-9 were further modified by the inclusion of a pre-incubation step. In this way, the range of mutagenic chemicals that can be detected using this assay system was increased. Following these treatments, no evidence of toxicity was observed with any of the test treatments.

Both the water and DMSO test article extracts were completely soluble in the aqueous assay system at all concentrations treated, in each of the experiments performed.

Negative (blank extraction vehicle) and positive control treatments were included for all strains with each extract vehicle in each experiment. The mean numbers of revertant colonies on negative control plates were all considered acceptable, and were significantly elevated by positive control treatments.

Following PIP silicone gel breast implant treatments of all the test strains in the absence and presence of S-9 using DMSO and water extracts, no increases in revertant numbers were observed that were statistically significant when the data were analysed at the 1% level using Dunnett's test. This study was considered therefore to have provided no evidence of any PIP silicone gel breast implant mutagenic activity in this assay system.

It was concluded that PIP silicone gel breast implant did not induce mutation in five histidine-requiring strains (TA98, TA100, TA1535, TA1537 and TA102) of *Salmonella typhimurium* when tested under the conditions of this study. These conditions included treatments using one organic vehicle (dimethyl sulphoxide, DMSO) and one aqueous vehicle (water) extracts of PIP silicone gel breast implant at concentrations up to maximum achievable concentrations of 20000 µg/plate (equivalent) (DMSO extract) or 100000 µg/plate (equivalent) (water extract), in the absence and in the presence of a rat liver metabolic activation system (S-9).

INTRODUCTION

The Ames test is a rapid, reliable and economical method of evaluating the mutagenic potential of a test article by measuring genetic activity in one or more histidine-requiring strains of *Salmonella typhimurium* in the absence and presence of a liver metabolising system [1]. A large database has been accumulated with this assay, confirming its ability to detect genetically active compounds of most chemical classes with around 80-90% sensitivity and specificity [2]. The following bacterial strains were used in this study:

Table 1: Bacterial Strains

Organism	Strain	Type of mutation in the histidine gene
S. typhimurium	TA98	frame-shift
S. typhimurium	TA100	base-pair substitution
S. typhimurium	TA1535	base-pair substitution
S. typhimurium	TA1537	frame-shift
S. typhimurium	TA102	base-pair substitution

With the exception of strain TA102, these strains require biotin as well as histidine for growth. In strain TA102 the critical mutation in the histidine gene is located on a multicopy plasmid pAQ1. This strain is particularly sensitive to the activities of oxidative and cross-linking mutagens. The pKM101 plasmid derivatives (TA98, TA100 and TA102) have increased sensitivity to certain mutagens as the pKM101 plasmid codes for an error-prone DNA repair system [3].

When exposed to a mutagen, some of the bacteria in the treated population, through chemical interaction with the compound, undergo genetic changes that revert them to a non-histidine-requiring state, and they can then grow without exogenous histidine. Different tester strains are used because each is mutated by particular chemical classes of compound. A compound that is mutagenic in one strain need not be so in another [4].

The objective of this study was therefore to evaluate the mutagenic activity of PIP silicone gel breast implant by examining its ability to revert five histidine-requiring strains of *Salmonella typhimurium* in the absence and in the presence of a rat liver metabolising system (S-9). The procedures used in this study were in accordance with OECD Guideline 471 (1997), UKEMS Guidelines (1990) and ICH Harmonised Tripartite Guideline (1995 and 1997). The test article comprised processed silicone gel breast implants, therefore was insoluble in all commonly used

vehicles. Extractions of the test article were therefore performed in order to permit testing in this assay system, and these extractions were conducted in accordance with the principles of ISO Guideline 10993, Part 3: 2003 and Part 12: 2007 ([5], [6]).

This study was performed according to the protocol and one amendment, with the exception of the minor deviations detailed in Appendix 9, none of which prejudiced the validity of this study.

The study was initiated on 19 July 2010. Experimental work started on 23 July 2010 and was completed on 10 August 2010. The study completion date is considered to be the date the Study Director signs the final report.

MATERIALS

Test article

PIP silicone gel breast implant, batch number 40709, was a clear white solid. Samples for testing were received on 14 July 2010 and stored at 15-25°C in the dark. The expiry date was given as November 2014. The test article information provided by the Sponsor is considered an adequate description of the characterisation and stability of the test article. Determinations of stability and characteristics of the test article were the responsibility of the Sponsor. Due to the nature of the test article (prosthetic implants) a specific purity value for this material is not considered appropriate.

Maximum concentrations of 20000 µg/plate (equivalent) (DMSO extract) and 100000 µg/plate (equivalent) (water extract) were selected for the Range-Finder Experiment, in order that initial treatments were performed up to the maximum achievable concentrations, and therefore compliant with the requirements of current regulatory guidelines ([2], [7], [8]). Maximum concentrations of 20000 µg/plate (equivalent) (DMSO extract) and 100000 µg/plate (equivalent) (water extract) were also selected for each subsequent experiment.

Each sample of the test article, PIP silicone gel breast implant, consists of an insoluble outer shell surrounding an insoluble silicone gel. As the test article is therefore insoluble in all commonly used vehicles, extracts of the test article were prepared according to the principles of ISO Guideline 10993, Part 3, 2003 and Part 12, 2007.

The test article was extracted in one polar (aqueous) vehicle (purified water) and one non-polar (organic) vehicle (sterile anhydrous analytical grade dimethyl sulphoxide, DMSO).

A PIP silicone gel breast implant was initially weighed, then pierced and the silicone gel and outer shell separated and each weighed, in order to estimate the proportion (by weight) of silicone gel to outer shell in the PIP silicone gel breast implant. This provided an estimated proportion of 8.43% outer shell to 91.57% inner silicone gel, and this proportion was used and applied for the amounts of outer shell and inner silicone gel weighed for all subsequent extractions. All operations were performed aseptically. An appropriate aliquot (91.57% of total extract material weight) of inner silicone gel was taken for extraction, and an appropriate amount (8.43% of total extract material weight) of the outer shell (cut into small pieces) added. Appropriate

extraction vehicle was added such that each extraction was performed at 200 mg/mL, and then extracted for 72 hours at 37°C, with shaking, in order to provide extracts that are considered an appropriate exaggeration of product use [6].

For each extraction vehicle, sufficient volumes of extract were prepared to treat the required strains on each experimental occasion, according to the volume additions detailed below. The resultant extracts were filter sterilised (using 0.2 or 0.22 µm pore size filter; see Minor deviations from protocol, Appendix 9) prior to treatment or dilution, and used on the day of completion of the extraction process.

Treatment volumes comprised 0.1 mL of DMSO extract or 0.5 mL of water extract, these being the maximum volumes tolerated by the assay system for each vehicle, and therefore allowed treatment up to maximum achievable concentrations. Extracts were diluted with the appropriate vehicle to provide a range of equivalent concentrations to be tested, as outlined below:

Table 2: PIP silicone gel breast implant Concentrations Tested – DMSO extract

Experiment	S-9	Concentration of treatment solution (mg/mL (equivalent))	Final concentration (µg/plate (equivalent))
Range-Finder Experiment and Mutation Experiment 1	- and +	0.064	6.4
		0.32	32
		1.60	160
		8.00	800
		40.00	4000
		200.00	20000
Mutation Experiment 2	- and +	6.25	625
		12.50	1250
		25.00	2500
		50.00	5000
		100.00	10000
		200.00	20000

Table 3: PIP silicone gel breast implant Concentrations Tested – Water extract

Experiment	S-9	Concentration of treatment solution (mg/mL (equivalent))	Final concentration (µg/plate (equivalent))
Range-Finder Experiment and Mutation Experiment 1	- and +	0.064	32
		0.32	160
		1.60	800
		8.00	4000
		40.00	20000
		200.00	100000
Mutation Experiment 2	- and +	6.25	3125
		12.50	6250
		25.00	12500
		50.00	25000
		100.00	50000
		200.00	100000

All concentrations should be considered as equivalent concentrations, based on 200 mg of test article being extracted per 1 mL of appropriate extraction vehicle.

Controls

Control treatments were performed using the same addition volumes per plate as the test article treatments, 0.1 mL for DMSO extracts and 0.5 mL for water extracts. Negative controls comprised treatments with the appropriate extraction vehicle (DMSO or purified water) carried through the same procedures used to extract the test article, including filter sterilisation (see Minor deviations from protocol, Appendix 9), and nominally referred to as blank extraction vehicle. The positive control chemicals were supplied and used according to the following table:

Table 4: Positive Controls

Chemical***	Stock * concentration (µg/mL)	Final concentration (µg/plate (equivalent))	Strain(s)	S-9
2-nitrofluorene (2NF)	50	5.0	TA98	–
Sodium azide (NaN_3)	20	2.0	TA100, TA1535	–
9-aminoacridine (AAC)	500	50.0	TA1537	–
Mitomycin C (MMC)	2	0.2	TA102	–
Benzo[a]pyrene (B[a]P)	100**	10.0	TA98	+
2-aminoanthracene (AAN)	50**	5.0	TA100, TA1535, TA1537	+
	200**	20.0	TA102	+

* Stock solutions were formulated in water (NaN_3 and MMC), or in DMSO (2NF, AAC, AAN and B[a]P). All stock solutions were stored in aliquots at 1-10°C in the dark, with the exception of B[a]P which was stored in aliquots at −80°C nominal, in the dark and MMC which was prepared freshly on the day of use or stored in aliquots at −80°C nominal in the dark.
** Concentrations were twice that stated for the pre-incubation methodology (0.05 mL per plate).
*** Obtained from Sigma-Aldrich Chemical Co, Poole, UK.

Metabolic activation system

The mammalian liver post-mitochondrial fraction (S-9) used for metabolic activation was obtained from Molecular Toxicology Incorporated, USA where it was prepared from male Sprague Dawley rats induced with Aroclor 1254. The batches of MolTox™ S-9 were stored frozen in aliquots at -80°C nominal, and thawed just prior to use [9]. Each batch was checked by the manufacturer for sterility, protein content, ability to convert ethidium bromide and cyclophosphamide to bacterial mutagens, and cytochrome P-450-catalysed enzyme activities (alkoxyresorufin-O-dealkylase activities). The quality control statement relating to the batch of S-9 preparation used is included in Appendix 8 of this report.

Treatments were carried out both in the absence and presence of a 10% S-9 mix, according to the following table (per 100 mL mix):

Table 5: Metabolic Activation System

Ingredient	Concentration	Quantity (mL)	
		10% S-9 mix	Buffer solution
Sodium phosphate buffer pH 7.4	500 mM	20	20
Glucose-6-phosphate (disodium)	180 mg/mL	0.845	–
β-Nicotinamide adenine dinucleotide phosphate (NADP) (disodium)	25 mg/mL	12.6	–
Magnesium chloride	250 mM	3.2	–
Potassium chloride	150 mM	22	–
L-histidine HCl (in 250 mM $MgCl_2$)	1 mg/mL	4	4
d-biotin	1 mg/mL	4.88	4.88
S-9	as detailed above	10	–
Water	–	to volume	to volume

Bacteria

Five strains of *Salmonella typhimurium* bacteria (TA98, TA100, TA1535, TA1537 and TA102) were used in this study. All the tester strains, with the exception of strain TA102, were originally obtained from the UK NCTC. Strain TA102 was derived from a culture obtained from Glaxo Group Research Limited. For all assays, bacteria were cultured at 37±1°C for 10 hours in nutrient broth, containing ampicillin (TA98, TA100) or ampicillin and tetracycline (TA102) as appropriate. Incubation was carried out with shaking in an anhydric incubator, set to turn on using a timer switch. All treatments were completed within 6 hours of the end of the incubation period.

The inocula were taken from master plates or vials of frozen cultures, which had been checked for strain characteristics (histidine dependence, *rfa* character, *uvrB* character and resistance to ampicillin or ampicillin plus tetracycline). Checks were carried out according to Maron and Ames [3] and De Serres and Shelby [10].

METHODS

Toxicity Range-Finder Experiment

PIP silicone gel breast implant was tested for toxicity (and mutation) in strain TA100, using water and DMSO extracts at the concentrations detailed previously. Triplicate plates without and with S-9 mix were used. Negative (blank extraction vehicle) and positive controls were included in quintuplicate and triplicate respectively, without and with S-9 mix. These platings were achieved by the following sequence of additions to 2.5 mL molten agar at 46±1°C:

- 0.1 mL bacterial culture
- 0.1 mL test article extract or control (DMSO) or
  0.5 mL test article extract or control (water)
- 0.5 mL 10% S-9 mix or buffer solution

followed by rapid mixing and pouring on to Vogel-Bonner E agar plates. When set, the plates were inverted and incubated at 37±1°C in the dark for 3 days. Following incubation, these plates were examined for evidence of toxicity to the background lawn, and where possible revertant colonies were counted (see Colony counting).

Mutation Experiments

PIP silicone gel breast implant was tested for mutation (and toxicity) in five strains of *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537 and TA102), in two separate experiments, using water and DMSO extracts at the concentrations detailed previously. Triplicate plates were tested without and with S-9. Experiment 1 mutagenicity data for strain TA100 were provided by the Range-Finder Experiment treatments. Negative (blank extraction vehicle) controls were included in quintuplicate, and positive controls were included in triplicate in both assays without and with S-9. Platings were achieved as described above.

As the results of Experiment 1 were negative, treatments in the presence of S-9 in Experiment 2 included a pre-incubation step. Quantities of test article or control solution, bacteria and S-9 mix detailed above, were mixed together and incubated for 1 hour at 37±1°C, before the addition of 2.5 mL molten agar at 46±1°C. Plating of these treatments then proceeded as for the normal plate-incorporation procedure. In this way, it was hoped to increase the range of mutagenic chemicals that could be detected in the assay.

Additions of 0.5 mL of 500 mM sodium phosphate buffer (pH 7.4) were employed for the DMSO extract and control treatments in Experiment 2, in order to reduce the solvent concentration during the pre-incubation period. DMSO, and some other organic solvents, are known to be near to toxic levels when added at volumes of 0.1 mL in this assay system when employing the pre-incubation methodology. By employing the modification indicated, the DMSO concentration in the pre-incubation mix was decreased, and it was hoped that this would minimise or eliminate any toxic effects of the solvent that may have otherwise occurred. In order to 'correct' for the additional volume in the pre-incubation mix, these were plated out using 2 mL of 1.125% soft agar, therefore the additions to each plate were comparable to that of the plate-incorporation treatments.

Colony counting

Colonies were counted electronically using a Sorcerer Colony Counter (Perceptive Instruments) or manually where confounding factors such as bubbles or splits in the agar affected the accuracy of the automated counter. The background lawn was inspected for signs of toxicity.

Analysis of results

Treatment of data

Individual plate counts from each vehicle extract in each experiment were recorded separately and the mean and standard deviation of the plate counts for each treatment were determined. Control counts were compared with the accepted normal ranges for our laboratory for numbers of spontaneous revertants on vehicle control plates (Appendix 6) and numbers of induced revertants on positive control plates (Appendix 7). Data were considered acceptable if the mean vehicle control counts fell within the historical 99% confidence intervals for group means and/or each vehicle control plate count fell within the historical 99% reference ranges, and the positive control plate counts were comparable with the historical 99% reference ranges. The ranges that are quoted are based on a large volume of historical control data accumulated from experiments where the correct strain and assay functioning are considered to have been confirmed. Data for our laboratory are consistent with ranges of spontaneous revertants per plate considered acceptable elsewhere [10].

For evaluation of test article and positive control data there are many statistical methods in use, and several are acceptable ([11], [12]). Dunnett's test was used to compare the counts at each concentration with the control. The presence or

otherwise of a concentration response was checked by non-statistical analysis, up to limiting levels (for example toxicity, precipitation or 5000 µg/plate (equivalent).

Acceptance criteria

The assay was considered valid if the following criteria were met:

1. the negative control counts fell within the normal ranges as defined in Appendix 6

2. the positive control chemicals induced clear increases in revertant numbers confirming discrimination between different strains, and an active S-9 preparation

3. no more than 5% of the plates were lost through contamination or some other unforeseen event.

Evaluation criteria

For valid data, the test article was considered to be mutagenic if:

1. Dunnett's test gave a significant response ($p \leq 0.01$) which was concentration related

2. the positive trend/effects described above were reproducible.

The test article was considered as positive in this assay if all of the above criteria were met with either or both vehicle extracts.

The test article was considered as negative in this assay if none of the above criteria were met with either vehicle extract.

RESULTS

Toxicity, solubility and concentration selection

Details of all treatment solution concentrations and final PIP silicone gel breast implant concentrations are provided in the Test article section.

An initial toxicity Range-Finder Experiment was carried out in the absence and in the presence of S-9 in strain TA100 only, using final concentrations of a DMSO extract of PIP silicone gel breast implant at 6.4, 32, 160, 800, 4000 and 20000 μg/plate (equivalent), and using final concentrations of a water extract of PIP silicone gel breast implant at 32, 160, 800, 4000, 20000 and 100000 μg/plate (equivalent), plus negative (blank extraction vehicle) and positive controls. Following these treatments, no evidence of toxicity was observed, as would normally be indicated by a diminution of the background bacterial lawn and/or a marked reduction in revertant numbers. These data were considered to be acceptable for mutation assessment and are presented in this report as the TA100 mutagenicity data for Experiment 1.

Experiment 1 treatments of the remaining tester strains with water and DMSO extracts of PIP silicone gel breast implant were performed in the absence and in the presence of S-9. The concentrations employed for the Range-Finder Experiment treatments were retained for Experiment 1. Following these treatments, no evidence of toxicity was observed.

Experiment 2 treatments of all the tester strains were performed in the absence and in the presence of S-9. The maximum test concentrations of 20000 μg/plate (equivalent) for the DMSO extract or 100000 μg/plate (equivalent) for the water extract were retained for all strains. Narrowed concentration intervals were employed covering the ranges 625 - 20000 μg/plate (equivalent) (DMSO extract) or 3125 - 100000 μg/plate (equivalent) (water extract), in order to examine more closely those concentrations of both water and DMSO extracts of PIP silicone gel breast implant approaching the maximum test concentrations, and considered therefore most likely to provide evidence of any mutagenic activity. In addition, all treatments in the presence of S-9 were further modified by the inclusion of a pre-incubation step. In this way, the range of mutagenic chemicals that could be detected using this assay system was increased. Following these treatments, no evidence of toxicity was observed.

Both the water and DMSO test article extracts were completely soluble in the aqueous assay system at all concentrations treated, in each of the experiments performed.

Data acceptability and validity

The individual plate counts were averaged to give mean values, which are presented in Appendix 1, Appendix 2, Appendix 3 and Appendix 4. From the data it can be seen that mean vehicle control counts with each vehicle were comparable with the normal historical ranges presented in Appendix 6 (see Minor deviations from protocol, Appendix 9). The positive control chemicals all induced large increases in revertant numbers in the appropriate strains, which were consistent with the normal historical ranges (Appendix 7). Less than 5% of plates were lost, leaving adequate numbers of plates at all treatments. The study therefore demonstrated correct strain and assay functioning and was accepted as valid.

Mutation

Following treatments of all the test strains with water and DMSO extracts PIP silicone gel breast implant in the absence and presence of S-9, no increases in revertant numbers were observed that were statistically significant when the data were analysed at the 1% level using Dunnett's test (Appendix 1, Appendix 2, Appendix 3 and Appendix 4). This study was considered therefore to have provided no evidence of any PIP silicone gel breast implant mutagenic activity in this assay system.

CONCLUSION

It was concluded that PIP silicone gel breast implant did not induce mutation in five histidine-requiring strains (TA98, TA100, TA1535, TA1537 and TA102) of *Salmonella typhimurium* when tested under the conditions of this study. These conditions included treatments using one organic vehicle (dimethyl sulphoxide, DMSO) and one aqueous vehicle (water) extracts of PIP silicone gel breast implant at concentrations up to maximum achievable concentrations of 20000 µg/plate (equivalent) (DMSO extract) or 100000 µg/plate (equivalent) (water extract), in the absence and in the presence of a rat liver metabolic activation system (S-9).

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APPENDICES

Appendix 1
Raw plate counts and calculated mutagenicity data Experiment 1 - DMSO Extract

Table 6: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 1 - DMSO Extract, TA98 –S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; DMSO		17, 29, 29, 22, 22	23.8	5		5.2		
PIP silicone gel breast implant ; DMSO extract	6.4	15, 24, 30	23.0	3	1.0	7.5	-0.25	NS
PIP silicone gel breast implant ; DMSO extract	32	30, 30, 27	29.0	3	1.2	1.7	1.27	NS
PIP silicone gel breast implant ; DMSO extract	160	26, 39, 29	31.3	3	1.3	6.8	1.73	NS
PIP silicone gel breast implant ; DMSO extract	800	17, 19, 22	19.3	3	0.8	2.5	-1.11	NS
PIP silicone gel breast implant ; DMSO extract	4000	16, 24, 10	16.7	3	0.7	7.0	-2.00	NS
PIP silicone gel breast implant ; DMSO extract	20000	27, 20, 26	24.3	3	1.0	3.8	0.16	NS
2NF	5	851, 778, 587	738.7	3	31.0	136.3		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 7: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 1 - DMSO Extract, TA98 +S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; DMSO		42, 46, 41, 37, 35	40.2	5		4.3		
PIP silicone gel breast implant ; DMSO extract	6.4	37, 31, 29	32.3	3	0.8	4.2	-1.83	NS
PIP silicone gel breast implant ; DMSO extract	32	42, 36, 34	37.3	3	0.9	4.2	-0.64	NS
PIP silicone gel breast implant ; DMSO extract	160	30, 37, 22	29.7	3	0.7	7.5	-2.56	NS
PIP silicone gel breast implant ; DMSO extract	800	31, 37, 45	37.7	3	0.9	7.0	-0.60	NS
PIP silicone gel breast implant ; DMSO extract	4000	40, 37, 36	37.7	3	0.9	2.1	-0.55	NS
PIP silicone gel breast implant ; DMSO extract	20000	32, 46, 51	43.0	3	1.1	9.8	0.54	NS
B[a]P	10	464, 461, 430	451.7	3	11.2	18.8		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 8: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 1 - DMSO Extract, TA100 -S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; DMSO		113, 139 M B, 120, 153, 142	133.4	5		16.5		
PIP silicone gel breast implant ; DMSO extract	6.4	154, 137, 133	141.3	3	1.1	11.2	0.89	NS
PIP silicone gel breast implant ; DMSO extract	32	142, 123, 153	139.3	3	1.0	15.2	0.66	NS
PIP silicone gel breast implant ; DMSO extract	160	140, 114, 123	125.7	3	0.9	13.2	-0.85	NS
PIP silicone gel breast implant ; DMSO extract	800	129, 135, 133	132.3	3	1.0	3.1	-0.07	NS
PIP silicone gel breast implant ; DMSO extract	4000	120, 128, 128	125.3	3	0.9	4.6	-0.86	NS
PIP silicone gel breast implant ; DMSO extract	20000	147, 125, 130	134.0	3	1.0	11.5	0.09	NS
NaN_3	2	477, 446, 445	456.0	3	3.4	18.2		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 9: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 1 - DMSO Extract, TA100 +S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; DMSO		129, 134, 153, 110, 114	128.0	5		17.2		
PIP silicone gel breast implant ; DMSO extract	6.4	138, 130, 130	132.7	3	1.0	4.6	0.54	NS
PIP silicone gel breast implant ; DMSO extract	32	123, 137, 138	132.7	3	1.0	8.4	0.53	NS
PIP silicone gel breast implant ; DMSO extract	160	143, 134, 129	135.3	3	1.1	7.1	0.81	NS
PIP silicone gel breast implant ; DMSO extract	800	144, 160, 130	144.7	3	1.1	15.0	1.74	NS
PIP silicone gel breast implant ; DMSO extract	4000	144, 144, 130	139.3	3	1.1	8.1	1.22	NS
PIP silicone gel breast implant ; DMSO extract	20000	108, 142, 137	129.0	3	1.0	18.4	0.11	NS
AAN	5	534, 699, 682	638.3	3	5.0	90.8		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 10: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 1 - DMSO Extract, TA1535 -S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; DMSO		17, 11, 9, 9, 15	12.2	5		3.6		
PIP silicone gel breast implant ; DMSO extract	6.4	17, 15, 14	15.3	3	1.3	1.5	1.07	NS
PIP silicone gel breast implant ; DMSO extract	32	10, 21, 12	14.3	3	1.2	5.9	0.65	NS
PIP silicone gel breast implant ; DMSO extract	160	17, 21, 11	16.3	3	1.3	5.0	1.29	NS
PIP silicone gel breast implant ; DMSO extract	800	20, 7, 14	13.7	3	1.1	6.5	0.37	NS
PIP silicone gel breast implant ; DMSO extract	4000	15, 9, 12	12.0	3	1.0	3.0	-0.04	NS
PIP silicone gel breast implant ; DMSO extract	20000	11, 15, 11	12.3	3	1.0	2.3	0.09	NS
NaN_3	2	405, 364, 403	390.7	3	32.0	23.1		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 11: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 1 - DMSO Extract, TA1535 +S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; DMSO		21, 11, 16, 12, 14	14.8	5		4.0		
PIP silicone gel breast implant ; DMSO extract	6.4	15, 9, 9	11.0	3	0.7	3.5	-1.55	NS
PIP silicone gel breast implant ; DMSO extract	32	6, 6, 9	7.0	3	0.5	1.7	-3.48	NS
PIP silicone gel breast implant ; DMSO extract	160	14, 10, 16	13.3	3	0.9	3.1	-0.55	NS
PIP silicone gel breast implant ; DMSO extract	800	10, 12, 12	11.3	3	0.8	1.2	-1.34	NS
PIP silicone gel breast implant ; DMSO extract	4000	20, 10, 9	13.0	3	0.9	6.1	-0.81	NS
PIP silicone gel breast implant ; DMSO extract	20000	14, 12, 12	12.7	3	0.9	1.2	-0.77	NS
AAN	5	189, 193, 213	198.3	3	13.4	12.9		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 12: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 1 - DMSO Extract, TA1537 -S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; DMSO		12, 16, 11, 11, 12	12.4	5		2.1		
PIP silicone gel breast implant ; DMSO extract	6.4	16, 15, 5	12.0	3	1.0	6.1	-0.38	NS
PIP silicone gel breast implant ; DMSO extract	32	6, 12, 10	9.3	3	0.8	3.1	-1.28	NS
PIP silicone gel breast implant ; DMSO extract	160	10, 11, 10	10.3	3	0.8	0.6	-0.79	NS
PIP silicone gel breast implant ; DMSO extract	800	10, 16, 6	10.7	3	0.9	5.0	-0.81	NS
PIP silicone gel breast implant ; DMSO extract	4000	11, 7, 7	8.3	3	0.7	2.3	-1.69	NS
PIP silicone gel breast implant ; DMSO extract	20000	11, 12, 12	11.7	3	0.9	0.6	-0.26	NS
AAC	50	92, 50, 65	69.0	3	5.6	21.3		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 13: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 1 - DMSO Extract, TA1537 +S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; DMSO		21, 16, 12, 19, 14	16.4	5		3.6		
PIP silicone gel breast implant ; DMSO extract	6.4	13 M B, 35, 26	24.7	3	1.5	11.1	1.70	NS
PIP silicone gel breast implant ; DMSO extract	32	19, 22, 25	22.0	3	1.3	3.0	1.32	NS
PIP silicone gel breast implant ; DMSO extract	160	20, 21, 20	20.3	3	1.2	0.6	0.97	NS
PIP silicone gel breast implant ; DMSO extract	800	15, 22, 17	18.0	3	1.1	3.6	0.40	NS
PIP silicone gel breast implant ; DMSO extract	4000	26, 19, 19	21.3	3	1.3	4.0	1.16	NS
PIP silicone gel breast implant ; DMSO extract	20000	7, 20, 24	17.0	3	1.0	8.9	-0.05	NS
AAN	5	66, 92, 80	79.3	3	4.8	13.0		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 14: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 1 - DMSO Extract, TA102 -S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; DMSO		206, 201, 226, 254, 221	221.6	5		20.8		
PIP silicone gel breast implant ; DMSO extract	6.4	172, 172, 137	160.3	3	0.7	20.2	-3.00	NS
PIP silicone gel breast implant ; DMSO extract	32	184, 193, 211	196.0	3	0.9	13.7	-1.18	NS
PIP silicone gel breast implant ; DMSO extract	160	257, 224, 206	229.0	3	1.0	25.9	0.33	NS
PIP silicone gel breast implant ; DMSO extract	800	208, 315, 242	255.0	3	1.2	54.7	1.40	NS
PIP silicone gel breast implant ; DMSO extract	4000	191, 216, 136	181.0	3	0.8	40.9	-1.99	NS
PIP silicone gel breast implant ; DMSO extract	20000	188, 157, 181	175.3	3	0.8	16.3	-2.21	NS
MMC	0.2	722, 715, 765	734.0	3	3.3	27.1		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 15: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 1 - DMSO Extract, TA102 +S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; DMSO		234, 298, 197, 202, 197	225.6	5		43.3		
PIP silicone gel breast implant ; DMSO extract	6.4	203, 221, 206	210.0	3	0.9	9.6	-0.84	NS
PIP silicone gel breast implant ; DMSO extract	32	179, 224, 206	203.0	3	0.9	22.6	-1.28	NS
PIP silicone gel breast implant ; DMSO extract	160	198, 202, 202	200.7	3	0.9	2.3	-1.40	NS
PIP silicone gel breast implant ; DMSO extract	800	208, 202, 201	203.7	3	0.9	3.8	-1.22	NS
PIP silicone gel breast implant ; DMSO extract	4000	196, 173, 191	186.7	3	0.8	12.1	-2.29	NS
PIP silicone gel breast implant ; DMSO extract	20000	178, 165, 182	175.0	3	0.8	8.9	-3.04	NS
AAN	20	854, 869, 861	861.3	3	3.8	7.5		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Appendix 2
Raw plate counts and calculated mutagenicity data Experiment 2 - DMSO Extract

Table 16: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 2 - DMSO Extract, TA98 –S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; DMSO		21, 21, 17, 16, 22	19.4	5		2.7		
PIP silicone gel breast implant ; DMSO extract	625	17, 14, 29	20.0	3	1.0	7.9	0.05	NS
PIP silicone gel breast implant ; DMSO extract	1250	30, 21, 41	30.7	3	1.6	10.0	2.73	*
PIP silicone gel breast implant ; DMSO extract	2500	22, 34, 25	27.0	3	1.4	6.2	1.94	NS
PIP silicone gel breast implant ; DMSO extract	5000	25, 30, 31	28.7	3	1.5	3.2	2.38	NS
PIP silicone gel breast implant ; DMSO extract	10000	22, 19, 26	22.3	3	1.2	3.5	0.80	NS
PIP silicone gel breast implant ; DMSO extract	20000	24, 24, 20	22.7	3	1.2	2.3	0.90	NS
2NF	5	914, 1155, 1118	1062.3	3	54.8	129.8		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 17: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 2 - DMSO Extract, TA98 +S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; DMSO		26, 40, 29, 34, 36	33.0	5		5.6		
PIP silicone gel breast implant ; DMSO extract	625	39, 30, 31	33.3	3	1.0	4.9	0.10	NS
PIP silicone gel breast implant ; DMSO extract	1250	31, 40, 26	32.3	3	1.0	7.1	-0.17	NS
PIP silicone gel breast implant ; DMSO extract	2500	31, 41, 30	34.0	3	1.0	6.1	0.24	NS
PIP silicone gel breast implant ; DMSO extract	5000	27, 27, 36	30.0	3	0.9	5.2	-0.72	NS
PIP silicone gel breast implant ; DMSO extract	10000	31, 47, 36	38.0	3	1.2	8.2	1.12	NS
PIP silicone gel breast implant ; DMSO extract	20000	30, 37, 32	33.0	3	1.0	3.6	0.03	NS
B[a]P	10	324, 310, 330	321.3	3	9.7	10.3		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 18: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 2 - DMSO Extract, TA100 -S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; DMSO		134 M B, 128, 141, 118, 102	124.6	5		15.2		
PIP silicone gel breast implant ; DMSO extract	625	98, 118, 118	111.3	3	0.9	11.5	-1.46	NS
PIP silicone gel breast implant ; DMSO extract	1250	108, 90, 108	102.0	3	0.8	10.4	-2.55	NS
PIP silicone gel breast implant ; DMSO extract	2500	102, 118, 113	111.0	3	0.9	8.2	-1.49	NS
PIP silicone gel breast implant ; DMSO extract	5000	107, 120, 130	119.0	3	1.0	11.5	-0.59	NS
PIP silicone gel breast implant ; DMSO extract	10000	88, 110, 113	103.7	3	0.8	13.7	-2.37	NS
PIP silicone gel breast implant ; DMSO extract	20000	125, 120, 135	126.7	3	1.0	7.6	0.26	NS
NaN_3	2	857, 774, 732	787.7	3	6.3	63.6		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 19: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 2 - DMSO Extract, TA100 +S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; DMSO		123, 111, 92, 100, 127	110.6	5		14.8		
PIP silicone gel breast implant ; DMSO extract	625	120, 128, 125	124.3	3	1.1	4.0	1.01	NS
PIP silicone gel breast implant ; DMSO extract	1250	107, 111, 116	111.3	3	1.0	4.5	0.08	NS
PIP silicone gel breast implant ; DMSO extract	2500	117, 116, 140	124.3	3	1.1	13.6	1.00	NS
PIP silicone gel breast implant ; DMSO extract	5000	142, 150, 80	124.0	3	1.1	38.3	0.84	NS
PIP silicone gel breast implant ; DMSO extract	10000	122, 121, 86	109.7	3	1.0	20.5	-0.09	NS
PIP silicone gel breast implant ; DMSO extract	20000	101, 126, 126	117.7	3	1.1	14.4	0.52	NS
AAN	5	1135, 1021, 1000	1052.0	3	9.5	72.6		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 20: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 2 - DMSO Extract, TA1535 -S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; DMSO		10, 20, 22, 10, 16	15.6	5		5.5		
PIP silicone gel breast implant ; DMSO extract	625	11, 6, 14	10.3	3	0.7	4.0	-1.59	NS
PIP silicone gel breast implant ; DMSO extract	1250	5, 7, 11	7.7	3	0.5	3.1	-2.54	NS
PIP silicone gel breast implant ; DMSO extract	2500	14, 14, 16	14.7	3	0.9	1.2	-0.15	NS
PIP silicone gel breast implant ; DMSO extract	5000	12, 12, 21	15.0	3	1.0	5.2	-0.13	NS
PIP silicone gel breast implant ; DMSO extract	10000	10, 26, 16	17.3	3	1.1	8.1	0.41	NS
PIP silicone gel breast implant ; DMSO extract	20000	14, 12, 14	13.3	3	0.9	1.2	-0.54	NS
NaN_3	2	511, 489, 511	503.7	3	32.3	12.7		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 21: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 2 - DMSO Extract, TA1535 +S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; DMSO		14, 11, 9, 10, 7	10.2	5		2.6		
PIP silicone gel breast implant ; DMSO extract	625	12, 2, 4	6.0	3	0.6	5.3	-1.91	NS
PIP silicone gel breast implant ; DMSO extract	1250	11, 9, 11	10.3	3	1.0	1.2	0.08	NS
PIP silicone gel breast implant ; DMSO extract	2500	14, 14, 10	12.7	3	1.2	2.3	0.81	NS
PIP silicone gel breast implant ; DMSO extract	5000	10, 20, 5	11.7	3	1.1	7.6	0.25	NS
PIP silicone gel breast implant ; DMSO extract	10000	14, 7, 12	11.0	3	1.1	3.6	0.24	NS
PIP silicone gel breast implant ; DMSO extract	20000	9, 10, 9	9.3	3	0.9	0.6	-0.26	NS
AAN	5	233, 201, 239	224.3	3	22.0	20.4		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 22: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 2 - DMSO Extract, TA1537 -S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; DMSO		7, 6, 17, 6, 9	9.0	5		4.6		
PIP silicone gel breast implant ; DMSO extract	625	9, 11, 10	10.0	3	1.1	1.0	0.54	NS
PIP silicone gel breast implant ; DMSO extract	1250	6, 6, 10	7.3	3	0.8	2.3	-0.59	NS
PIP silicone gel breast implant ; DMSO extract	2500	5, 5, 10	6.7	3	0.7	2.9	-0.92	NS
PIP silicone gel breast implant ; DMSO extract	5000	11, 4, 4	6.3	3	0.7	4.0	-1.18	NS
PIP silicone gel breast implant ; DMSO extract	10000	10, 6, 10	8.7	3	1.0	2.3	-0.02	NS
PIP silicone gel breast implant ; DMSO extract	20000	7, 2, 6	5.0	3	0.6	2.6	-1.82	NS
AAC	50	137, 186, 147	156.7	3	17.4	25.9		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 23: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 2 - DMSO Extract, TA1537 +S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; DMSO		20, 16, 6, 24, 20	17.2	5		6.9		
PIP silicone gel breast implant ; DMSO extract	625	12, 10, 17	13.0	3	0.8	3.6	-1.06	NS
PIP silicone gel breast implant ; DMSO extract	1250	19, 17, 20	18.7	3	1.1	1.5	0.58	NS
PIP silicone gel breast implant ; DMSO extract	2500	12, 12, 11	11.7	3	0.7	0.6	-1.44	NS
PIP silicone gel breast implant ; DMSO extract	5000	20, 22, 20	20.7	3	1.2	1.2	1.09	NS
PIP silicone gel breast implant ; DMSO extract	10000	25, 17, 16	19.3	3	1.1	4.9	0.71	NS
PIP silicone gel breast implant ; DMSO extract	20000	21, 11, 22	18.0	3	1.0	6.1	0.31	NS
AAN	5	136, 202, 226	188.0	3	10.9	46.6		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 24: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 2 - DMSO Extract, TA102 -S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; DMSO		229, 243, 249, 278, 247	249.2	5		17.9		
PIP silicone gel breast implant ; DMSO extract	625	248, 283, 238	256.3	3	1.0	23.6	0.46	NS
PIP silicone gel breast implant ; DMSO extract	1250	227, 289, 289	268.3	3	1.1	35.8	1.19	NS
PIP silicone gel breast implant ; DMSO extract	2500	277, 288, 251	272.0	3	1.1	19.0	1.46	NS
PIP silicone gel breast implant ; DMSO extract	5000	275, 292, 268	278.3	3	1.1	12.3	1.86	NS
PIP silicone gel breast implant ; DMSO extract	10000	283, 243, 236	254.0	3	1.0	25.4	0.30	NS
PIP silicone gel breast implant ; DMSO extract	20000	248, 254, 256	252.7	3	1.0	4.2	0.24	NS
MMC	0.2	779, 698, 695	724.0	3	2.9	47.7		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 25: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 2 - DMSO Extract, TA102 +S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; DMSO		269, 278, 217, 269, 229	252.4	5		27.4		
PIP silicone gel breast implant ; DMSO extract	625	218, 237, 243	232.7	3	0.9	13.1	-1.38	NS
PIP silicone gel breast implant ; DMSO extract	1250	242, 244, 253	246.3	3	1.0	5.9	-0.39	NS
PIP silicone gel breast implant ; DMSO extract	2500	288, 272, 270	276.7	3	1.1	9.9	1.70	NS
PIP silicone gel breast implant ; DMSO extract	5000	290, 243, 279	270.7	3	1.1	24.6	1.28	NS
PIP silicone gel breast implant ; DMSO extract	10000	294, 307, 284	295.0	3	1.2	11.5	2.91	*
PIP silicone gel breast implant ; DMSO extract	20000	208, 177, 214	199.7	3	0.8	19.9	-3.90	NS
AAN	20	2042, 2438, 1853	2111.0	3	8.4	298.5		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Appendix 3
Raw plate counts and calculated mutagenicity data Experiment 1 - Water Extract

Table 26: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 1 - Water Extract, TA98 –S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; Water		26, 39, 17, 29, 31	28.4	5		8.0		
PIP silicone gel breast implant; Water extract	32	19, 34, 37	30.0	3	1.1	9.6	0.27	NS
PIP silicone gel breast implant; Water extract	160	12, 20, 15	15.7	3	0.6	4.0	-2.55	NS
PIP silicone gel breast implant; Water extract	800	14, 24, 22	20.0	3	0.7	5.3	-1.59	NS
PIP silicone gel breast implant; Water extract	4000	22, 16, 32	23.3	3	0.8	8.1	-0.95	NS
PIP silicone gel breast implant; Water extract	20000	22, 17, 26	21.7	3	0.8	4.5	-1.22	NS
PIP silicone gel breast implant; Water extract	100000	27, 26, 15	22.7	3	0.8	6.7	-1.06	NS
2NF	5	1123, 1091, 1269	1161.0	3	40.9	94.9		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 27: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 1 - Water Extract, TA98 +S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; Water		37, 27, 31, 19, 31	29.0	5		6.6		
PIP silicone gel breast implant; Water extract	32	35, 29, 37	33.7	3	1.2	4.2	0.94	NS
PIP silicone gel breast implant; Water extract	160	39, 37, 45	40.3	3	1.4	4.2	2.12	NS
PIP silicone gel breast implant; Water extract	800	34, 42, 25	33.7	3	1.2	8.5	0.89	NS
PIP silicone gel breast implant; Water extract	4000	27, 19, 30	25.3	3	0.9	5.7	-0.74	NS
PIP silicone gel breast implant; Water extract	20000	25, 47, 34	35.3	3	1.2	11.1	1.16	NS
PIP silicone gel breast implant; Water extract	100000	24, 39, 31	31.3	3	1.1	7.5	0.46	NS
B[a]P	10	418, 317, 408	381.0	3	13.1	55.7		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 28: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 1 - Water Extract, TA100 - S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; Water		148, 110, 140, 128, 139 M B	133.0	5		14.7		
PIP silicone gel breast implant; Water extract	32	98, 120, 134	117.3	3	0.9	18.1	-1.56	NS
PIP silicone gel breast implant; Water extract	160	120, 138, 109	122.3	3	0.9	14.6	-1.04	NS
PIP silicone gel breast implant; Water extract	800	117, 123, 113	117.7	3	0.9	5.0	-1.48	NS
PIP silicone gel breast implant; Water extract	4000	144, 133, 147	141.3	3	1.1	7.4	0.81	NS
PIP silicone gel breast implant; Water extract	20000	140, 123, 142	135.0	3	1.0	10.4	0.21	NS
PIP silicone gel breast implant; Water extract	100000	139, 146 M B, 110	131.7	3	1.0	19.1	-0.14	NS
NaN_3	2	550, 406, 467	474.3	3	3.6	72.3		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 29: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 1 - Water Extract, TA100 +S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; Water		140, 124, 100, 132, 135	126.2	5		15.8		
PIP silicone gel breast implant; Water extract	32	115, 130, 109	118.0	3	0.9	10.8	-0.74	NS
PIP silicone gel breast implant; Water extract	160	170, 138, 139	149.0	3	1.2	18.2	2.00	NS
PIP silicone gel breast implant; Water extract	800	123, 128, 152	134.3	3	1.1	15.5	0.74	NS
PIP silicone gel breast implant; Water extract	4000	103, 118, 145	122.0	3	1.0	21.3	-0.40	NS
PIP silicone gel breast implant; Water extract	20000	139, 153, 124	138.7	3	1.1	14.5	1.13	NS
PIP silicone gel breast implant; Water extract	100000	135, 132, 138	135.0	3	1.1	3.0	0.83	NS
AAN	5	541, 693, 776	670.0	3	5.3	119.2		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 30: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 1 - Water Extract, TA1535 -S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; Water		22, 22, 17, 12, 15	17.6	5		4.4		
PIP silicone gel breast implant; Water extract	32	9, 10, 6	8.3	3	0.5	2.1	-3.14	NS
PIP silicone gel breast implant; Water extract	160	6, 9, 16	10.3	3	0.6	5.1	-2.46	NS
PIP silicone gel breast implant; Water extract	800	17, 12, 10	13.0	3	0.7	3.6	-1.41	NS
PIP silicone gel breast implant; Water extract	4000	6, 6, 14	8.7	3	0.5	4.6	-3.11	NS
PIP silicone gel breast implant; Water extract	20000	10, 15, 20	15.0	3	0.9	5.0	-0.80	NS
PIP silicone gel breast implant; Water extract	100000	16, 15, 14	15.0	3	0.9	1.0	-0.72	NS
NaN_3	2	487, 348, 465	433.3	3	24.6	74.7		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 31: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 1 - Water Extract, TA1535 +S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; Water		9, 12, 10, 11, 15	11.4	5		2.3		
PIP silicone gel breast implant; Water extract	32	26, 12, 22	20.0	3	1.8	7.2	2.92	*
PIP silicone gel breast implant; Water extract	160	17, 10, 16	14.3	3	1.3	3.8	1.10	NS
PIP silicone gel breast implant; Water extract	800	15, 15, 16	15.3	3	1.3	0.6	1.53	NS
PIP silicone gel breast implant; Water extract	4000	11, 20, 22	17.7	3	1.5	5.9	2.21	NS
PIP silicone gel breast implant; Water extract	20000	17, 14, 11	14.0	3	1.2	3.0	1.01	NS
PIP silicone gel breast implant; Water extract	100000	10, 12, 11	11.0	3	1.0	1.0	-0.14	NS
AAN	5	202, 218, 232	217.3	3	19.1	15.0		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 32: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 1 - Water Extract, TA1537 -S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; Water		10, 11, 10, 10, 11	10.4	5		0.5		
PIP silicone gel breast implant; Water extract	32	4, 5, 7	5.3	3	0.5	1.5	-3.95	NS
PIP silicone gel breast implant; Water extract	160	12, 9, 9	10.0	3	1.0	1.7	-0.29	NS
PIP silicone gel breast implant; Water extract	800	10, 10, 5	8.3	3	0.8	2.9	-1.57	NS
PIP silicone gel breast implant; Water extract	4000	6, 6, 9	7.0	3	0.7	1.7	-2.51	NS
PIP silicone gel breast implant; Water extract	20000	11, 15, 12	12.7	3	1.2	2.1	1.39	NS
PIP silicone gel breast implant; Water extract	100000	10, 6, 10	8.7	3	0.8	2.3	-1.27	NS
AAC	50	65, 71, 75	70.3	3	6.8	5.0		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 33: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 1 - Water Extract, TA1537 +S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; Water		20, 14, 14, 20, 17	17.0	5		3.0		
PIP silicone gel breast implant; Water extract	32	15, 21, 19	18.3	3	1.1	3.1	0.56	NS
PIP silicone gel breast implant; Water extract	160	19, 12, 19	16.7	3	1.0	4.0	-0.17	NS
PIP silicone gel breast implant; Water extract	800	12, 15, 14	13.7	3	0.8	1.5	-1.46	NS
PIP silicone gel breast implant; Water extract	4000	21, 20, 16	19.0	3	1.1	2.6	0.84	NS
PIP silicone gel breast implant; Water extract	20000	19, 20, 11	16.7	3	1.0	4.9	-0.21	NS
PIP silicone gel breast implant; Water extract	100000	15, 17, 15	15.7	3	0.9	1.2	-0.54	NS
AAN	5	57, 55, 59	57.0	3	3.4	2.0		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 34: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 1 - Water Extract, TA102 -S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; Water		207, 231, 260, 254 M B, 206	231.6	5		25.3		
PIP silicone gel breast implant; Water extract	32	290, 274, 263	275.7	3	1.2	13.6	1.79	NS
PIP silicone gel breast implant; Water extract	160	246, 280 M B, 295	273.7	3	1.2	25.1	1.70	NS
PIP silicone gel breast implant; Water extract	800	277, 254, 238	256.3	3	1.1	19.6	1.03	NS
PIP silicone gel breast implant; Water extract	4000	253, 257, 226	245.3	3	1.1	16.9	0.58	NS
PIP silicone gel breast implant; Water extract	20000	216, 252, 226	231.3	3	1.0	18.6	0.00	NS
PIP silicone gel breast implant; Water extract	100000	236, 199, 113	182.7	3	0.8	63.1	-2.34	NS
MMC	0.2	664, 612, 512	596.0	3	2.6	77.3		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 35: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 1 - Water Extract, TA102 +S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; Water		211, 234, 233, 237, 183	219.6	5		22.9		
PIP silicone gel breast implant; Water extract	32	262, 237, 222	240.3	3	1.1	20.2	0.94	NS
PIP silicone gel breast implant; Water extract	160	209, 231, 191	210.3	3	1.0	20.0	-0.42	NS
PIP silicone gel breast implant; Water extract	800	187, 166, 257	203.3	3	0.9	47.6	-0.82	NS
PIP silicone gel breast implant; Water extract	4000	188, 182, 227	199.0	3	0.9	24.4	-0.97	NS
PIP silicone gel breast implant; Water extract	20000	209, 202, 160	190.3	3	0.9	26.5	-1.40	NS
PIP silicone gel breast implant; Water extract	100000	192, 224, 268	228.0	3	1.0	38.2	0.36	NS
AAN	20	826, 765, 786	792.3	3	3.6	31.0		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Appendix 4
Raw plate counts and calculated mutagenicity data Experiment 2 - Water Extract

Table 36: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 2 - Water Extract, TA98 –S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; Water		22, 29, 22, 24, 27	24.8	5		3.1		
PIP silicone gel breast implant; Water extract	3125	14, 16, 20	16.7	3	0.7	3.1	-2.77	NS
PIP silicone gel breast implant; Water extract	6250	17, 15, 24	18.7	3	0.8	4.7	-2.07	NS
PIP silicone gel breast implant; Water extract	12500	22, 26, 32	26.7	3	1.1	5.0	0.54	NS
PIP silicone gel breast implant; Water extract	25000	25, 27, 25	25.7	3	1.0	1.2	0.29	NS
PIP silicone gel breast implant; Water extract	50000	15, 20, 26	20.3	3	0.8	5.5	-1.51	NS
PIP silicone gel breast implant; Water extract	100000	19, 12, 21	17.3	3	0.7	4.7	-2.57	NS
2NF	5	704, 545, 682	643.7	3	26.0	86.2		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 37: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 2 - Water Extract, TA98 +S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; Water		31, 21, 27, 39, 20	27.6	5		7.8		
PIP silicone gel breast implant; Water extract	3125	24, 24, 42	30.0	3	1.1	10.4	0.46	NS
PIP silicone gel breast implant; Water extract	6250	35, 30, 39	34.7	3	1.3	4.5	1.44	NS
PIP silicone gel breast implant; Water extract	12500	17, 22, 25	21.3	3	0.8	4.0	-1.31	NS
PIP silicone gel breast implant; Water extract	25000	25, 17, 22	21.3	3	0.8	4.0	-1.31	NS
PIP silicone gel breast implant; Water extract	50000	19, 19, 34	24.0	3	0.9	8.7	-0.78	NS
PIP silicone gel breast implant; Water extract	100000	31, 34, 37	34.0	3	1.2	3.0	1.32	NS
B[a]P	10	391, 450, 450	430.3	3	15.6	34.1		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 38: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 2 - Water Extract, TA100 -S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; Water		133, 115, 143, 110, 148	129.8	5		16.8		
PIP silicone gel breast implant; Water extract	3125	128, 125, 131	128.0	3	1.0	3.0	-0.10	NS
PIP silicone gel breast implant; Water extract	6250	160, 85, 107	117.3	3	0.9	38.6	-1.05	NS
PIP silicone gel breast implant; Water extract	12500	120, 123, 135	126.0	3	1.0	7.9	-0.25	NS
PIP silicone gel breast implant; Water extract	25000	137, 108, 120	121.7	3	0.9	14.6	-0.59	NS
PIP silicone gel breast implant; Water extract	50000	111, 132, 105	116.0	3	0.9	14.2	-1.02	NS
PIP silicone gel breast implant; Water extract	100000	111, 137, 122	123.3	3	1.0	13.1	-0.46	NS
NaN_3	2	521, 487, 403	470.3	3	3.6	60.7		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 39: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 2 - Water Extract, TA100 +S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; Water		122, 142, 131 M B, 141, 125	132.2	5		9.1		
PIP silicone gel breast implant; Water extract	3125	123, 88, 106	105.7	3	0.8	17.5	-2.43	NS
PIP silicone gel breast implant; Water extract	6250	120, 165, 113	132.7	3	1.0	28.2	-0.03	NS
PIP silicone gel breast implant; Water extract	12500	138, 121, 136	131.7	3	1.0	9.3	-0.04	NS
PIP silicone gel breast implant; Water extract	25000	110, 138, 107	118.3	3	0.9	17.1	-1.24	NS
PIP silicone gel breast implant; Water extract	50000	120, 105, 118	114.3	3	0.9	8.1	-1.58	NS
PIP silicone gel breast implant; Water extract	100000	131, 138, 108	125.7	3	1.0	15.7	-0.58	NS
AAN	5	597, 627, 649	624.3	3	4.7	26.1		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 40: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 2 - Water Extract, TA1535 -S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; Water		16, 7, 21, 19, 10	14.6	5		5.9		
PIP silicone gel breast implant; Water extract	3125	9, 15, 16	13.3	3	0.9	3.8	-0.21	NS
PIP silicone gel breast implant; Water extract	6250	2, 7, 16	8.3	3	0.6	7.1	-1.81	NS
PIP silicone gel breast implant; Water extract	12500	21, 15, 7	14.3	3	1.0	7.0	-0.08	NS
PIP silicone gel breast implant; Water extract	25000	17, 12, 9	12.7	3	0.9	4.0	-0.38	NS
PIP silicone gel breast implant; Water extract	50000	19, 15, 9	14.3	3	1.0	5.0	-0.01	NS
PIP silicone gel breast implant; Water extract	100000	15, 17, 12	14.7	3	1.0	2.5	0.12	NS
NaN_3	2	535, 566, 385	495.3	3	33.9	96.8		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 41: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 2 - Water Extract, TA1535 +S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; Water		7, 22, 4, 9, 17 M B	11.8	5		7.5		
PIP silicone gel breast implant; Water extract	3125	22, 15, 11	16.0	3	1.4	5.6	1.00	NS
PIP silicone gel breast implant; Water extract	6250	15, 7, 4	8.7	3	0.7	5.7	-0.68	NS
PIP silicone gel breast implant; Water extract	12500	2, 14, 6	7.3	3	0.6	6.1	-1.14	NS
PIP silicone gel breast implant; Water extract	25000	5, 4, 11	6.7	3	0.6	3.8	-1.16	NS
PIP silicone gel breast implant; Water extract	50000	4, 5, 9	6.0	3	0.5	2.6	-1.32	NS
PIP silicone gel breast implant; Water extract	100000	6, 9, 17	10.7	3	0.9	5.7	-0.15	NS
AAN	5	106, 132, 110	116.0	3	9.8	14.0		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 42: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 2 - Water Extract, TA1537 -S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; Water		7, 11, 6, 15, 9	9.6	5		3.6		
PIP silicone gel breast implant; Water extract	3125	10, 11, 7	9.3	3	1.0	2.1	-0.05	NS
PIP silicone gel breast implant; Water extract	6250	11, 6, 10	9.0	3	0.9	2.6	-0.25	NS
PIP silicone gel breast implant; Water extract	12500	9, 7, 9	8.3	3	0.9	1.2	-0.53	NS
PIP silicone gel breast implant; Water extract	25000	14, 7, 9	10.0	3	1.0	3.6	0.22	NS
PIP silicone gel breast implant; Water extract	50000	7, 5, 5	5.7	3	0.6	1.2	-2.08	NS
PIP silicone gel breast implant; Water extract	100000	9, 5, 10	8.0	3	0.8	2.6	-0.78	NS
AAC	50	145, 115, 117	125.7	3	13.1	16.8		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 43: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 2 - Water Extract, TA1537 +S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; Water		19, 27, 21, 17, 9	18.6	5		6.5		
PIP silicone gel breast implant; Water extract	3125	17, 22, 17	18.7	3	1.0	2.9	0.12	NS
PIP silicone gel breast implant; Water extract	6250	7, 5, 9	7.0	3	0.4	2.0	-3.15	NS
PIP silicone gel breast implant; Water extract	12500	5, 20, 20	15.0	3	0.8	8.7	-1.02	NS
PIP silicone gel breast implant; Water extract	25000	10, 16, 21	15.7	3	0.8	5.5	-0.65	NS
PIP silicone gel breast implant; Water extract	50000	16, 12, 10	12.7	3	0.7	3.1	-1.38	NS
PIP silicone gel breast implant; Water extract	100000	15, 12, 11	12.7	3	0.7	2.1	-1.36	NS
AAN	5	145, 136, 150	143.7	3	7.7	7.1		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 44: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 2 - Water Extract, TA102 -S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; Water		284, 340, 289, 253, 325	298.2	5		34.6		
PIP silicone gel breast implant; Water extract	3125	305, 325, 297	309.0	3	1.0	14.4	0.56	NS
PIP silicone gel breast implant; Water extract	6250	257, 257, 272	262.0	3	0.9	8.7	-1.79	NS
PIP silicone gel breast implant; Water extract	12500	337, 312, 317	322.0	3	1.1	13.2	1.18	NS
PIP silicone gel breast implant; Water extract	25000	318, 287, 315	306.7	3	1.0	17.1	0.44	NS
PIP silicone gel breast implant; Water extract	50000	319, 229, 278	275.3	3	0.9	45.1	-1.16	NS
PIP silicone gel breast implant; Water extract	100000	278, 260, 318	285.3	3	1.0	29.7	-0.62	NS
MMC	0.2	708, 990, 982	893.3	3	3.0	160.6		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Table 45: PIP silicone gel breast implant Raw plate counts and calculated mutagenicity data - Experiment 2 - Water Extract, TA102 +S-9

Compound	Concentration (µg/plate (equivalent))	Revertant numbers/plate	Mean	N	Fold Increase	Standard Deviation	Dunnett's t-value	Significance
Blank extraction vehicle; Water		201, 262, 183, 192, 228	213.2	5		32.1		
PIP silicone gel breast implant; Water extract	3125	251, 170, 181	200.7	3	0.9	43.9	-0.53	NS
PIP silicone gel breast implant; Water extract	6250	107, 193, 202	167.3	3	0.8	52.4	-2.02	NS
PIP silicone gel breast implant; Water extract	12500	219, 186, 197	200.7	3	0.9	16.8	-0.47	NS
PIP silicone gel breast implant; Water extract	25000	188, 226, 214	209.3	3	1.0	19.4	-0.13	NS
PIP silicone gel breast implant; Water extract	50000	181, 204, 223	202.7	3	1.0	21.0	-0.40	NS
PIP silicone gel breast implant; Water extract	100000	203, 165, 160	176.0	3	0.8	23.5	-1.52	NS
AAN	20	733, 406, 604	581.0	3	2.7	164.7		

For key to abbreviations, postfixes and significance values refer to Appendix 5

Appendix 5
Key to abbreviations, postfixes and significance values

Dunnett's t-test significance values

NS	Not significant
*	$p \leq 0.05$
**	$p \leq 0.01$

Positive controls

2NF	2-Nitrofluorene
NaN_3	Sodium azide
AAC	9-Aminoacridine
MMC	Mitomycin C
B[a]P	Benzo[a]pyrene
AAN	2-Aminoanthracene

Table Postfixes

B	Bubbles or split in agar
M	Plate counted manually

Appendix 6
Historical negative (vehicle) control values for *S. typhimurium* strains

Table 46: Historical negative (vehicle) control values for *S. typhimurium* strains

					Revertant numbers for individual plates			
						99% confidence interval for group mean of:		
Strain	S-9	No. of studies	No. of plates	Mean	99% reference range[1]	4 values [2]	5 values [2]	6 values [2]
TA98	-	50	503	25	10.0-43.0	16.4-33.3	17.1-32.3	17.7-31.5
TA98	+	50	525	35	15.0-56.0	24.7-46.2	25.6-44.9	26.4-44.0
TA100	-	50	572	111	72.0-160.0	88.8-134.1	90.9-131.5	92.6-129.6
TA100	+	50	588	119	77.0-178.0	92.9-145.4	95.4-142.4	97.2-140.1
TA1535	-	50	505	17	5.0-33.0	9.8-24.8	10.4-23.9	10.9-23.2
TA1535	+	50	524	19	6.0-35.0	11.6-26.8	12.2-25.9	12.7-25.2
TA1537	-	50	512	11	2.0-27.0	5.4-17.7	5.9-16.9	6.2-16.3
TA1537	+	50	534	15	4.0-32.0	8.3-22.9	8.9-21.9	9.4-21.2
TA102	-	48	475	281	178.0-435.0	222.8-342.7	228.5-335.7	232.7-330.6
TA102	+	48	499	238	152.0-341.0	194.4-283.4	198.7-278.3	201.9-274.6

[1] Reference ranges are calculated from percentiles of the observed distributions.
[2] Calculated from square-root transformed data.

Ranges calculated in August 2008 by CLEH Statistics, using data selected without bias from studies# started during the periods given below:

S.typhimurium strains (except TA102)	Mar 07 to Oct 07
S.typhimurium strain TA102	Feb 07 to Oct 07

All studies had been audited prior to data collection.

Appendix 7
Historical positive control values for *S. typhimurium* strains

Table 47: Historical positive control values for *S. typhimurium* strains

Strain	S-9	No. of studies	No. of plates	Induced numbers for individual plates: Mean	Reference ranges[1]: 95%	Reference ranges[1]: 99%
TA98	-	50	297	1331	654.8-1950.8	426.7-2215.8
TA98	+	50	309	345	189.0-529.4	157.0-681.6
TA100	-	50	339	750	450.8-1006.0	322.5-1056.0
TA100	+	50	348	1090	258.4-1801.8	85.4-1964.2
TA1535	-	50	297	638	352.3-925.0	204.8-1480.0
TA1535	+	50	309	257	53.6-458.6	45.0-806.0
TA1537	-	50	303	269	70.8-977.0	50.8-2396.2
TA1537	+	50	312	110	25.4-227.4	17.8-276.8
TA102	-	48	285	412	203.2-729.6	187.2-858.6
TA102	+	48	300	1055	317.0-2065.4	192.0-2529.4

[1] Reference ranges are calculated from percentiles of the observed distributions.

Ranges calculated in August 2008 by CLEH Statistics, using data selected without bias from studies# started during the periods given below:

S.typhimurium strains (except TA102) Mar 07 to Oct 07
S.typhimurium strain TA102 Feb 07 to Oct 07

All studies had been audited prior to data collection.

Appendix 8
Quality control statement for S-9

MOLTOX POST MITOCHONDRIAL SUPERNATANT (S-9)
QUALITY CONTROL & PRODUCTION CERTIFICATE

LOT NO.: 2595 **SPECIES:** Rat **PREPARATION DATE:** May 13, 2010
PART NO.: 11-101 **STRAIN:** Sprague Dawley **EXPIRATION DATE:** May 13, 2012
VOLUME: 5 ml **SEX:** Male **BUFFER:** 0.154 M KCl
TISSUE: Liver **INDUCING AGENT(s):** Aroclor 1254 (Monsanto KL615), 500 mg/kg i.p.
REFERENCE: Maron, D & Ames, B, *Mutat Res* **113**:173, 1983
STORAGE: At or below -70°C

BIOCHEMISTRY:

- PROTEIN

34.9 mg/ml

Assayed according to the method of Lowry et al., *JBC* **193**:265, 1951 using bovine serum albumin as the standard.

- ALKOXYRESORUFIN-0-DEALKYLASE ACTIVITIES

Activity	P450	Fold - Induction
EROD	1A1, 1A2	135.2
PROD	2B1, 2B2	30.2
BROD	2B1, 2B2	48.8
MROD	1A1, 1A2	138.7

Assays for ethoxyresorufin-0-deethylase (EROD), pentoxy-, benzyl- and methoxyresorufin-0-dealkylases (PROD, BROD, & MROD) were conducted using a modification of the methods of Burke, et al., *Biochem Pharm* **34**:3337, 1985. Fold-inductions were calculated as the ratio of the sample vs. uninduced specific activities (SA's). Control SA's (pmoles/min/mg protein) were 29.2, 15.9, 27.8, & 8.7 for EROD, PROD, BROD and MROD, respectively.

BIOASSAY:

- TEST FOR THE PRESENCE OF ADVENTITIOUS AGENTS

Samples of S-9 were assayed for the presence of contaminating microflora by plating 1.0 ml volumes on Nutrient Agar and Minimal Glucose (Vogel-Bonner E, supplemented with 0.05 mM L-histidine and D-biotin) media. Triplicate plates were read after 40 - 48 h incubation at 35 ± 2°C. The tested samples met acceptance criteria.

- PROMUTAGEN ACTIVATION

No. His+ Revertants	
TA98	TA1535
119.6	1412

The ability of the sample to activate ethidium (EtBr) EtBr/CPA/and cyclophosphamide (CPA) to intermediates mutagenic to TA98 and TA1535, respectively, was determined according to Lesca, et al., *Mutation Res* **129**:299, 1984. Data were expressed as revertants per µg EtBr or per mg CPA.

Dilutions of the sample S9, ranging from 0.2 - 10% in S9 mix, were tested for their ability to activate benzo(a)pyrene (BP) and 2-aminoanthracene (2-AA) to intermediates mutagenic to TA100. Assays were conducted as described by Maron & Ames, (*Mutat Res* **113**:173, 1983).

µl S9 per plate/number *his*$^+$ revertants per plate

Promutagen	0	1	5	10	20	50
BP (5 µg)	128	228	402	486	582	833
2-AA (2.5 µg)	117	620	1400	2008	1104	1074

MOLECULAR TOXICOLOGY, INC.
157 Industrial Park Dr.
Boone, NC 28607
(828) 264-9099
www.moltox.com

Approved: [redacted] 5/18/10

Appendix 9
Minor deviations from protocol

Protocol section	Subject	Deviation
Materials	Test Article	During the extraction procedure, all water extracts (test article and blank extracts) were filtered through a 0.22 µm filter, rather than a 0.2 µm filter as specified in the protocol. The 0.22 µm and 0.2 µm filter sizes are considered to be equivalent for the purpose required in this study, which were to filter-sterilise the test article and blank extracts, and this deviation from the extraction procedure is not considered to have had any impact on the resulting extract solutions or on the validity of the assay.
Materials	Controls	The protocol indicated that negative controls would comprise the appropriate extraction vehicle carried through the same procedures used to extract the test article. For the Range-Finder experiment extractions, the set-up of blank extraction vehicles was initially overlooked and these (blank) vehicle extractions were set up some 3.5 hours after the test article extractions. As a consequence, these (blank) vehicle extractions only received approximately 68.5 hours extraction rather than the 72 hours extraction that the test article extracts received. This relatively small difference in extraction time for the vehicle control treatments in the range-finder experiment is not considered to have had any adverse effect on the validity of this study.
Acceptance criteria	Vehicle control counts	For the Experiment 2 treatments of strain TA1535 in the presence of S-9 (water extract), the mean vehicle control count was marginally below the 99% confidence interval of the historical ranges, and the one replicate plate count was also below the 99% historical reference range. However, the mean vehicle control count was sufficiently comparable to the historical control range, and all individual replicate counts were within or close to reference range, that the correct strain and assay functioning was considered to have been confirmed. These strain data were therefore considered both acceptable and valid.

Definitive Final Report

Study Title	Extraction and organic analysis of implants
Authors(s)	[redacted]
Sponsor	Medicines and Healthcare products Regulatory Agency Market Towers 1 Nine Elms Lane LONDON SW8 5NQ
Sponsor Representative	[redacted]
Test Facility	Covance Laboratories Ltd Otley Road, Harrogate North Yorkshire HG3 1PY United Kingdom
Covance Sponsor Number	1008167
Covance Study Number	8232-400
Covance Report Number	D4005-8232-400
Report Issued	August 2010
Page Number	1 of 51

RESPONSIBLE ANALYST AUTHENTICATION AND COMPLIANCE STATEMENT

Extraction and organic analysis of implants

I, the undersigned, hereby declare that the work described in this final report was performed under my supervision, as Responsible Analyst, and that this final report provides a true and accurate record of the results obtained.

This study was performed in accordance with the agreed protocol, unless otherwise stated, and the study objectives for this phase of the study were achieved. This phase of the study was also performed in accordance with Covance Standard Operating Procedures and in accordance with the current version of the:

United Kingdom GMP Guidelines

The procedures in this phase of the study were also performed to the standards required by the current versions of the:

United Kingdom GLP Regulations

and the:

OECD GLP Principles

[redacted]

[redacted]
Responsible Analyst
Covance Laboratories Ltd

31/AUG/2010
Date

RESPONSIBLE PERSONNEL

Extraction and organic analysis of implants

The following staff were responsible for key elements of the study:

Analyst	[redacted]
	[redacted]

ARCHIVE STATEMENT

Extraction and organic analysis of implants

All primary data, or authenticated copies thereof, and result reports will be retained in the Covance archives for one year after issue of the final set of results. At this time, the Sponsor will be contacted to determine whether the data should be returned, retained or destroyed on their behalf.

NB archiving of examples of the reference standards and samples, if required, will be the responsibility of the Sponsor.

CONTENTS

SUMMARY

The objective of the study is to develop an extraction procedure for the gels from the supplied implants and analyse the resulting extracts for organic components using gas chromatography with mass selective detection (GC-MSD). General purpose analytical methods will be used to detect any organic components from the extracts.

Head-space GC-MS will be carried out directly on samples of the implant gel to assess volatile organic components.

Detected components, where possible, have been identified by comparison of their mass spectra with those from Wiley7/Nist05 libraries. Limited quantification of individual components from the head-space GC-MS method has been carried out using the internal standard, pentane, as quantification standard.

Details of the GC-MSD methods are provided in Appendix 1.

METHODS

Solvent based extracts

Initially on receipt of the samples, one implant was opened by cutting and removing the implant cover. Samples were taken from the gel and the remainder of the gel stored at controlled room temperature in a sealed container.

Samples of the gel, approx. 2 g were transferred to glass vials and 5 mL of a range of water immiscible solvents were added. The solvents used were: - chloroform, cyclohexane, dichloromethane, ethyl acetate, n-heptane and toluene. The vials were shaken by hand for approx. 10 sec and allowed to stand. The gel was not dispersed by the solvents, so a further 5 mL of solvent was added. No improvement in the dispersion of the gel was seen.

Water (10 mL) was added to all vials and the vials shaken and allowed to stand. Phase separation was obtained from all samples, but the water/solvent mixtures did not fully disperse the gel.

Logbook G867

A second batch of extracts was prepared from the same gel using the following solvents: - chloroform, dichloromethane, ethyl acetate, n-heptane and toluene. Approx. 2 g of gel was added

to 10 mL of solvent. The samples were shaken for 30 minutes on an horizontal shaker at 200 cycles/min. The extracts were allowed to stand and approx. 1 mL was transferred to a GC vial and capped for analysis by GC-MS. Control blanks were assayed for each of the solvents.

Method detail is given in Appendix 1.

The obtained chromatograms were integrated and each peak was compared with Wiley07/Nist05 libraries to obtain, were possible, an identification. Where no suitable match was found the peak was classified as un-identified. The mass to charge ratios (m/z) of the spectral peaks was listed in decreasing order of abundance.

Log book G867 Sequence G20100727B

Direct head-space analysis

Approx. 2 g of gel was transferred to a 20 mL head-space vial and capped securely. The internal standard, pentane dissolved in methanol (1 µL) was added using a calibrated syringe and needle via the septa. Control blanks were prepared from sealed head-space vials with pentane as above. The vials were transferred to the head-space attachment for GC-MS analysis.

Method detail is given in Appendix 1.

Log book G867 Sequence G20100727A

The obtained chromatograms were integrated and each peak was compared with Wiley07/Nist05 libraries to obtain, were possible, an identification. Where no suitable match was found the peak was classified as un-identified. The mass to charge ratios (m/z) of the spectral peaks was listed in decreasing order of abundance.

RESULTS

The results are given in Table 1 with a list of peak number, retention time, spectra number assessed, peak identification from Wiley7/Nist05 library and comments. Results are given in Tables 1 to 6.

FIGURES

Figure 1 Chloroform extract full scale

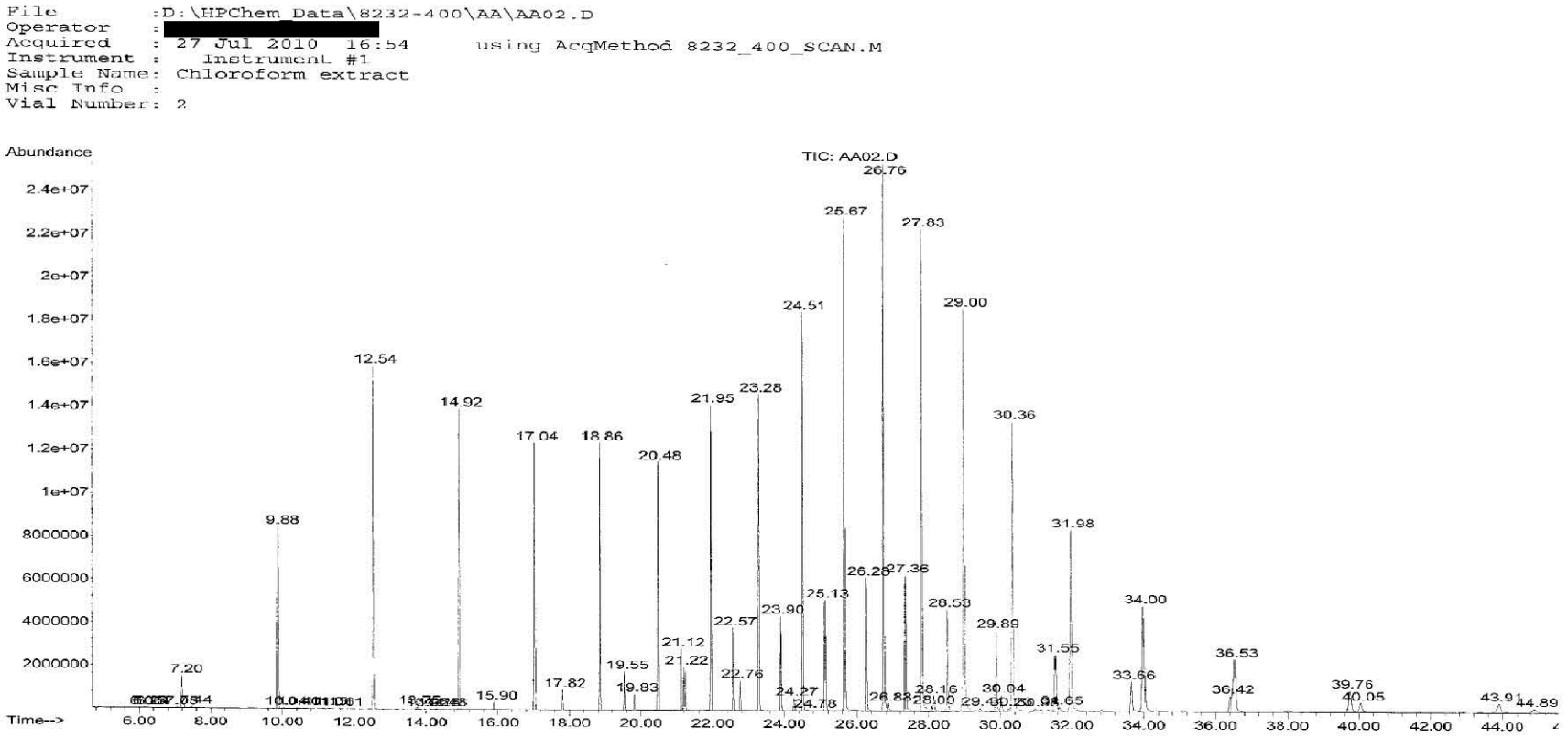

Figure 2 Chloroform extract expanded scale (1)

```
File        :D:\HPChem Data\8232-400\AA\AA02.D
Operator    :[redacted]
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Instrument :   Instrument #1
Sample Name: Chloroform extract
Misc Info  :
Vial Number: 2
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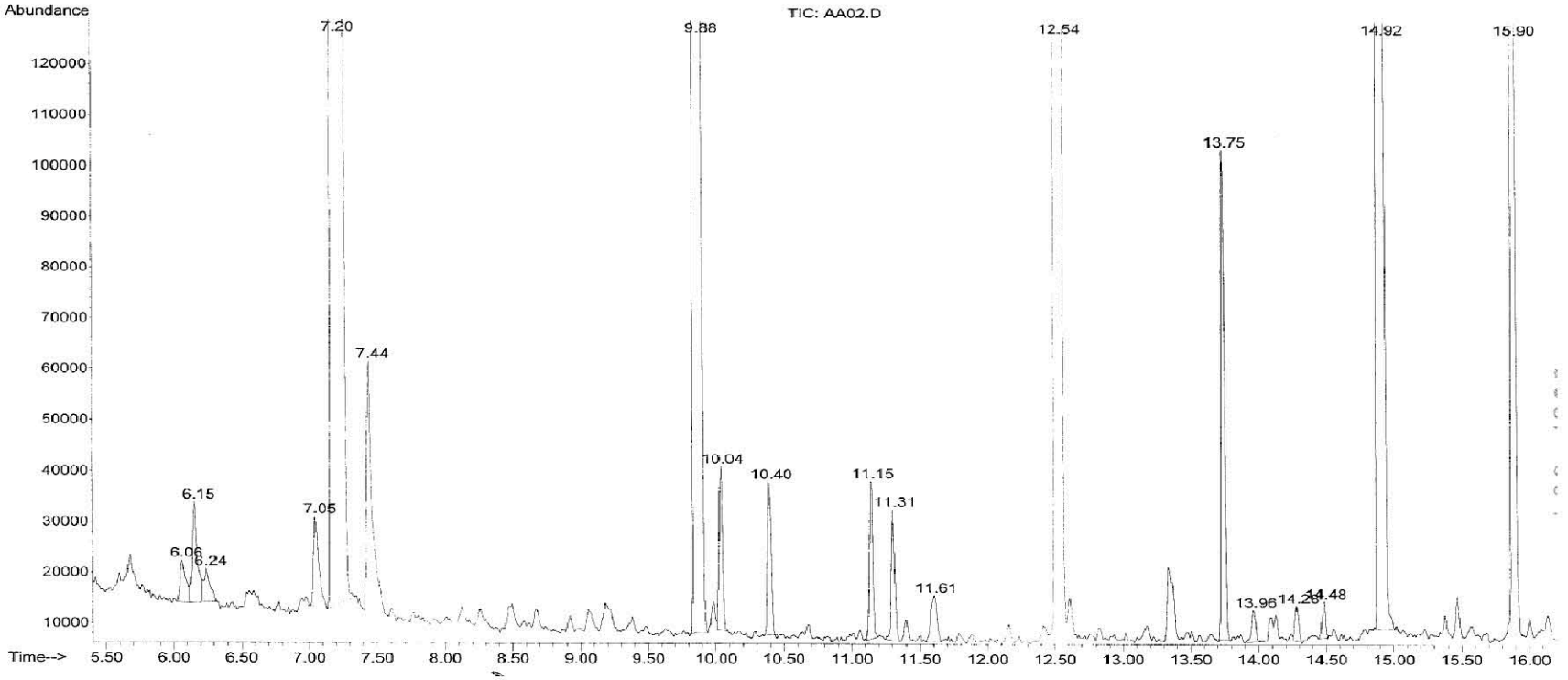

Figure 3 Chloroform extract expanded scale (2)

```
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Operator   : [redacted]
Acquired   : 27 Jul 2010  16:54      using AcqMethod 8232_400_SCAN.M
Instrument :   Instrument #1
Sample Name: Chloroform extract
Misc Info  :
Vial Number: 2
```

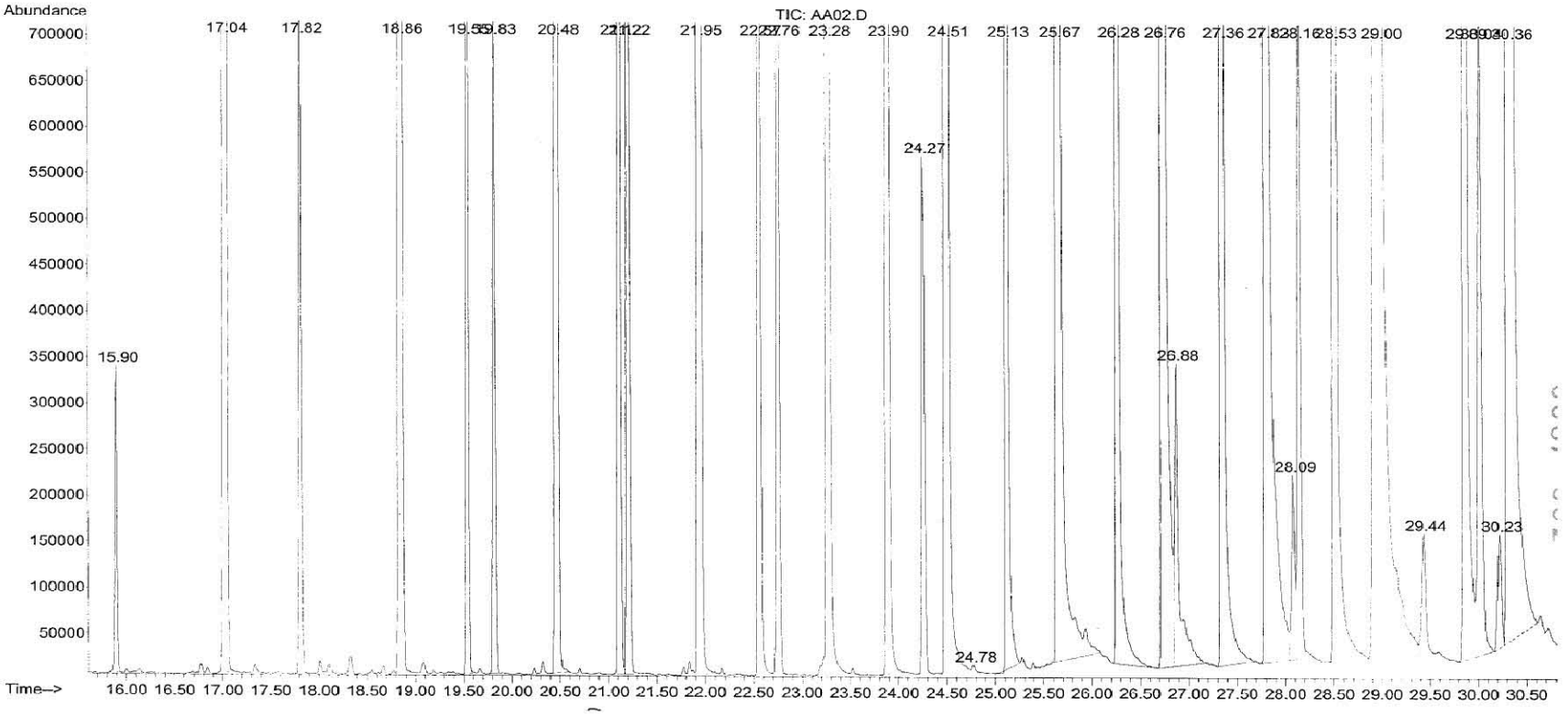

Figure 4 Chloroform extract expanded scale (3)

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Acquired : 27 Jul 2010 16:54 using AcqMethod 8232_400_SCAN.M
Instrument : Instrument #1
Sample Name: Chloroform extract
Misc Info :
Vial Number: 2

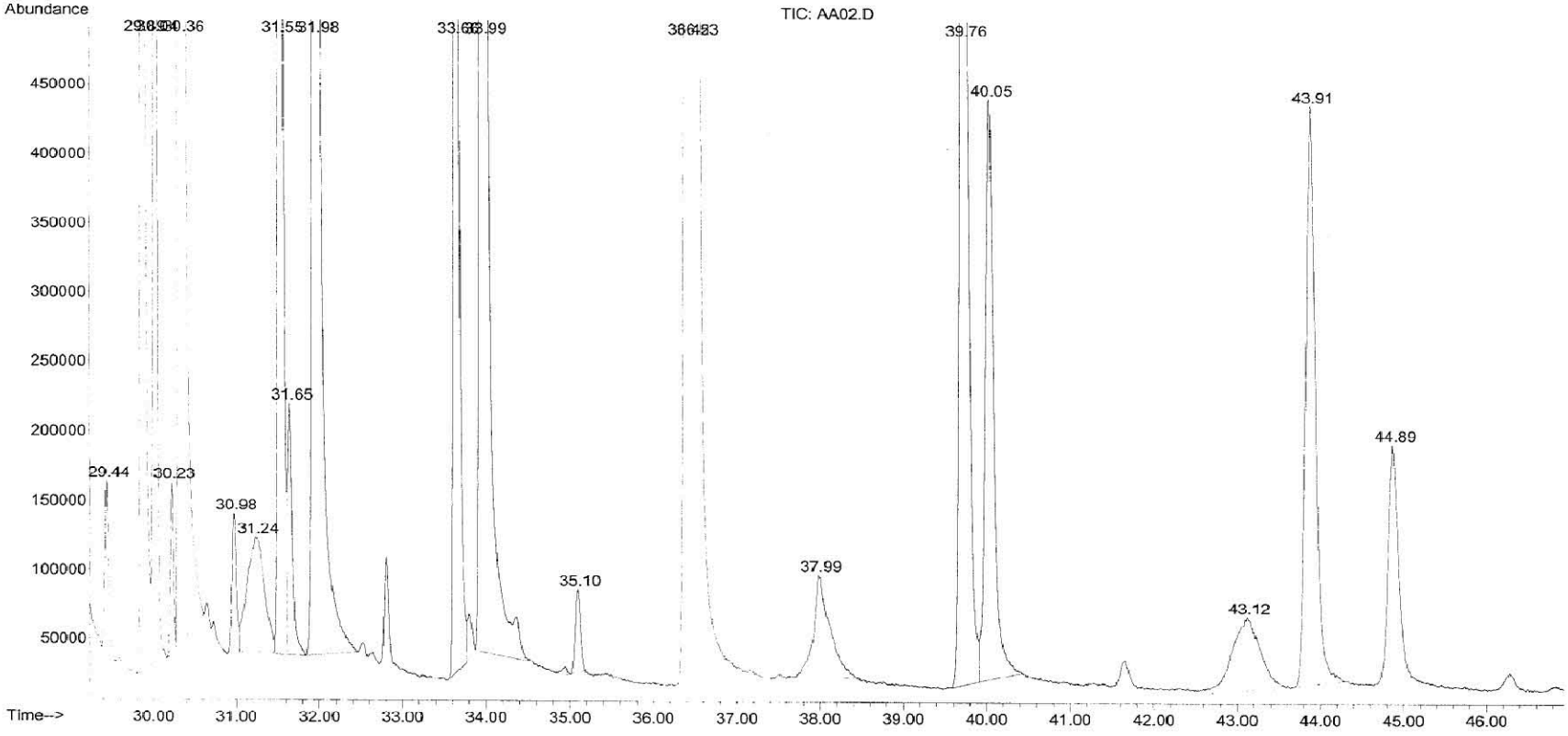

Figure 5 Dichloromethane extract full scale

```
File        :D:\HPChem Data\8232-400\AA\AA04.D
Operator    :
Acquired    : 27 Jul 2010  18:49      using AcqMethod 8232_400_SCAN.M
Instrument  :   Instrument #1
Sample Name: DCM extract
Misc Info   :
Vial Number: 4
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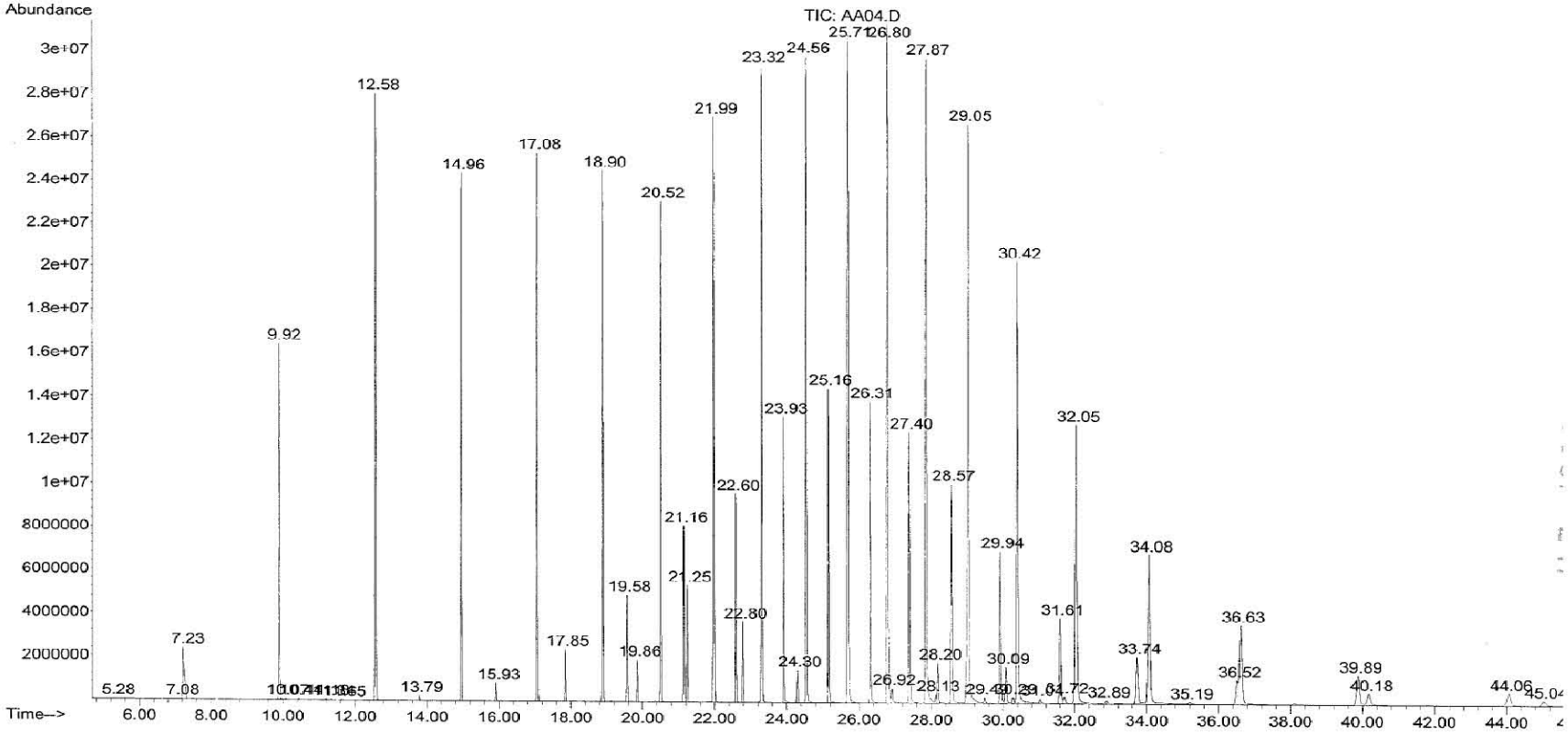

Figure 6 Dichloromethane extract expanded scale (1)

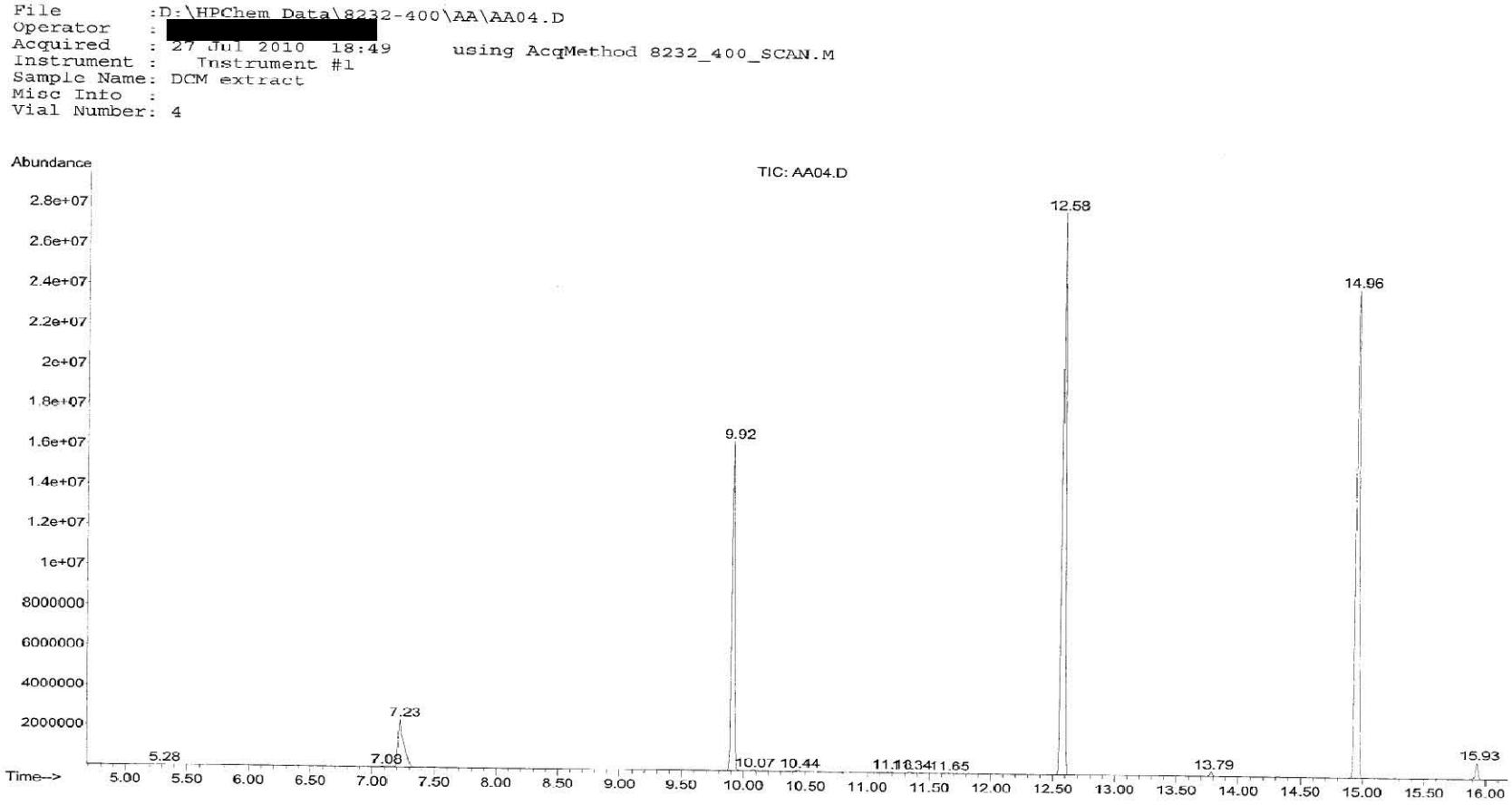

Figure 7 Dichloromethane extract expanded scale (2)

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Instrument : Instrument #1
Sample Name: DCM extract
Misc Info :
Vial Number: 4

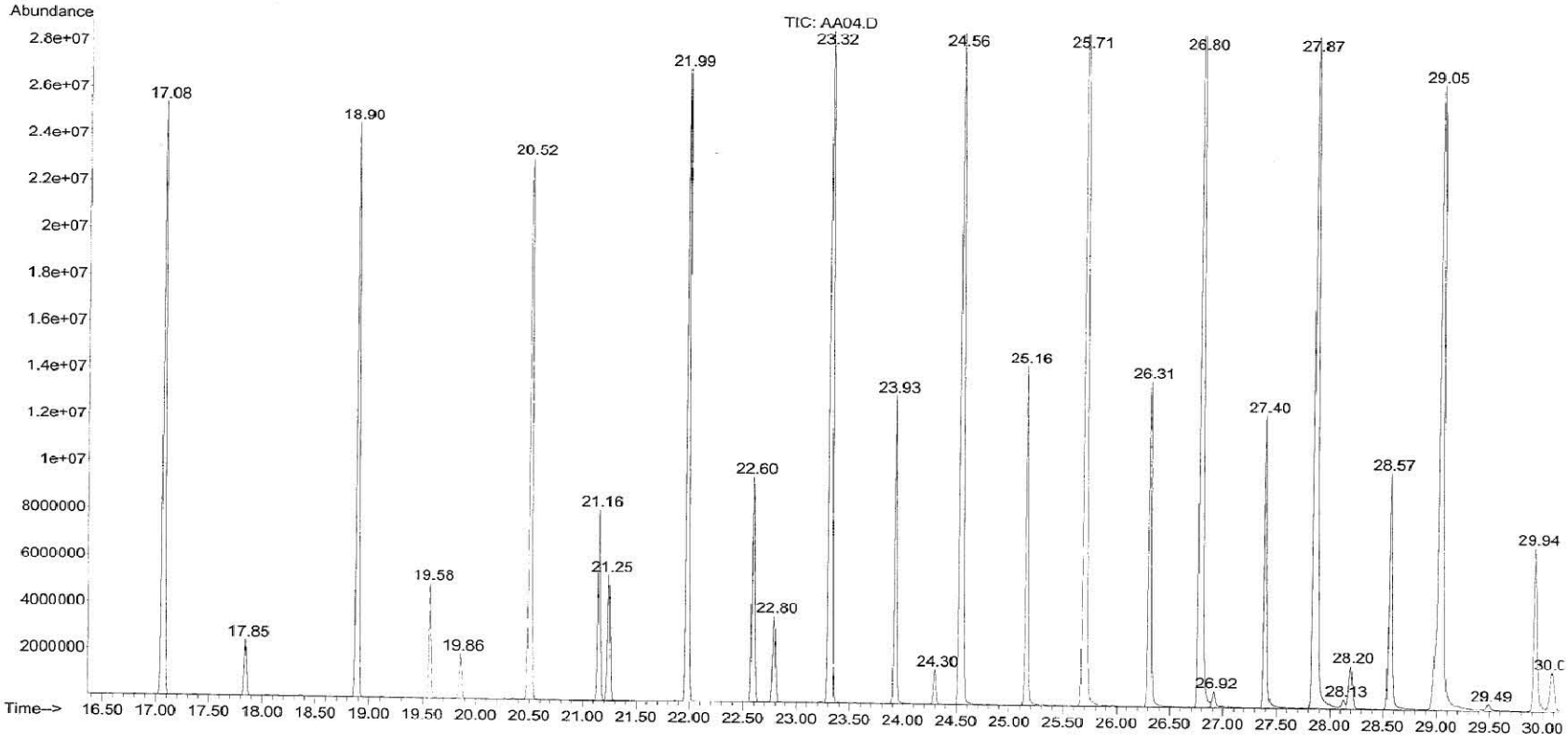

Figure 8 Dichloromethane extract expanded scale (3)

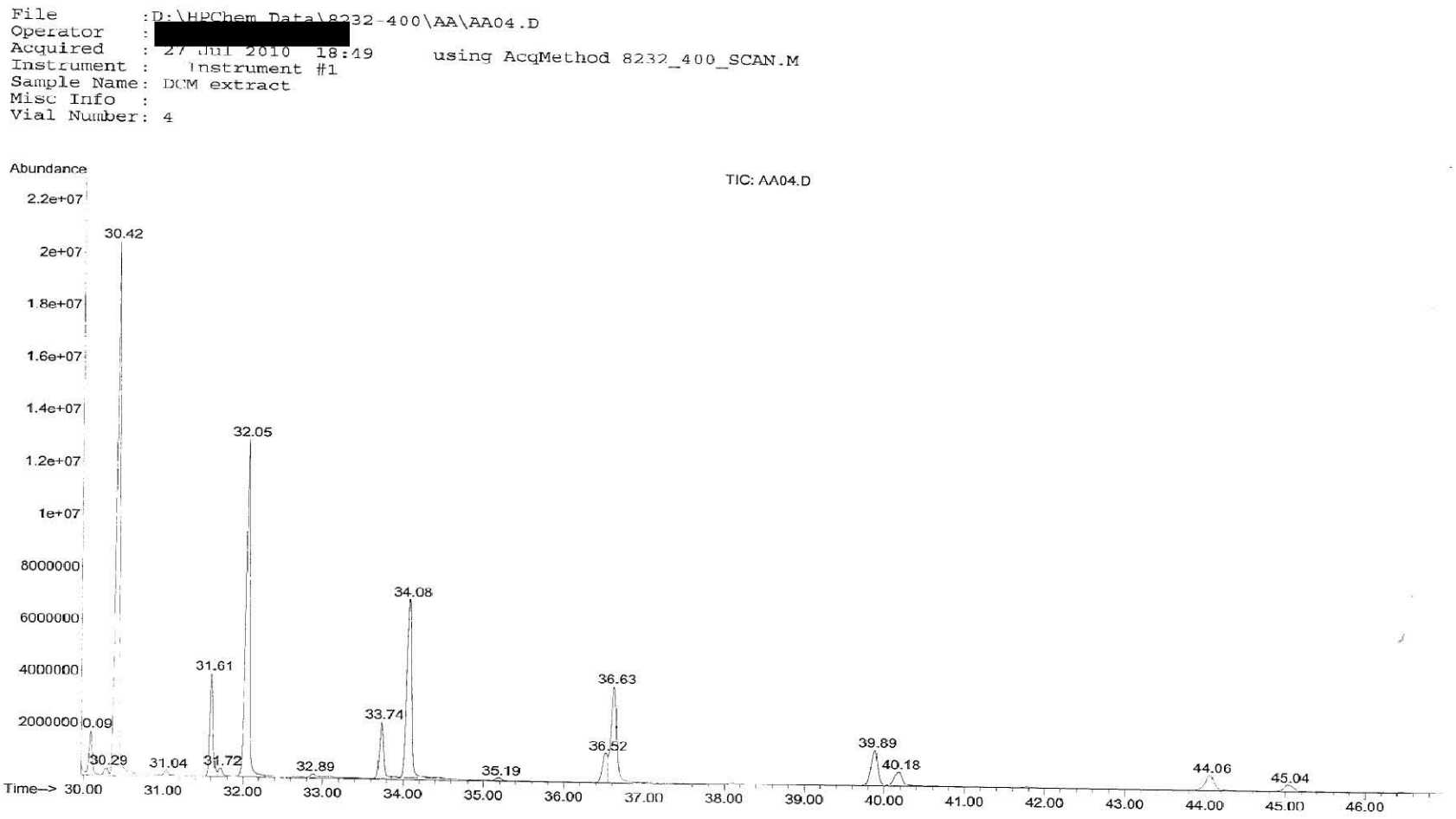

Figure 9 Ethyl acetate extract full scale

```
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Operator    : [redacted]
Acquired    : 27 Jul 2010  20:44      using AcqMethod 8232_400_SCAN.M
Instrument  :   Instrument #1
Sample Name: Ethyl acetate extract
Misc Info   :
Vial Number: 6
```

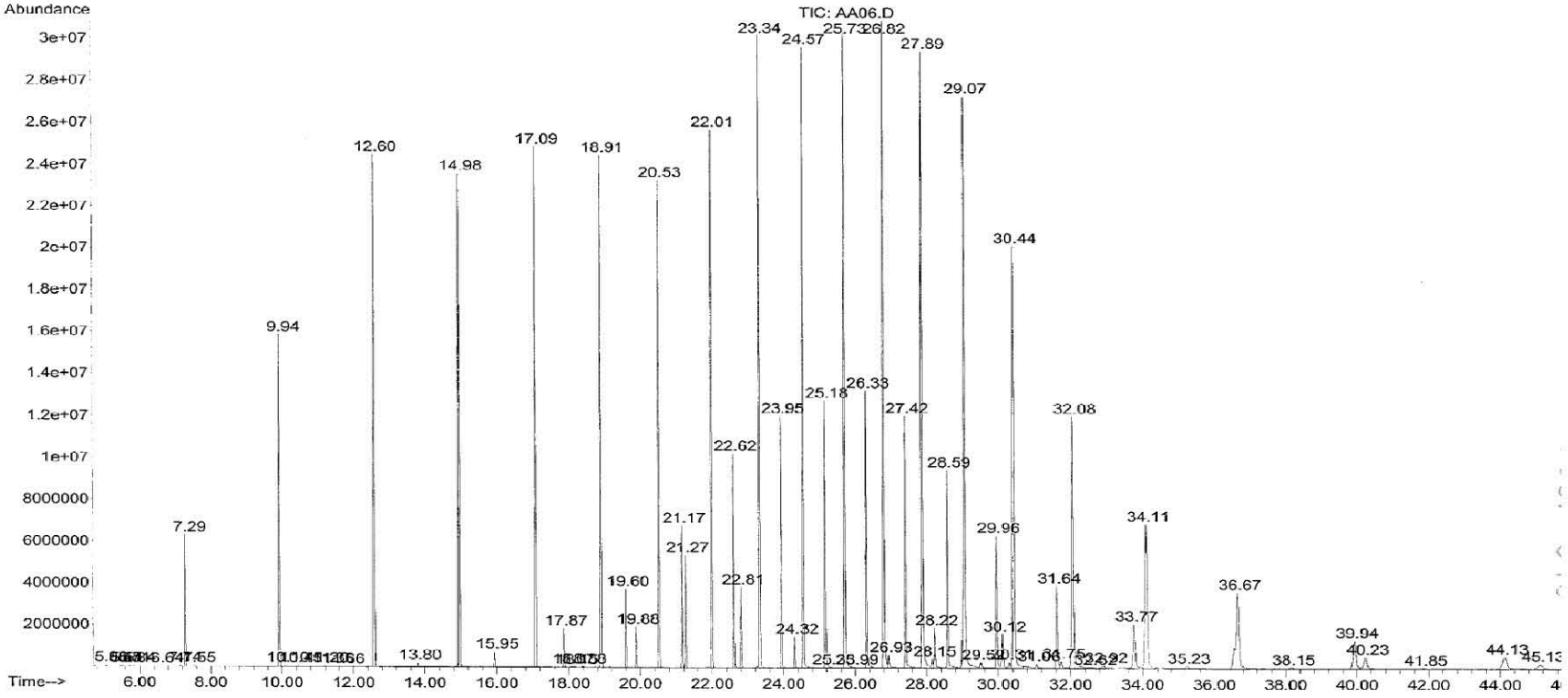

Figure 10 Ethyl acetate extract expanded scale (1)

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Instrument : Instrument #1
Sample Name: Ethyl acetate extract
Misc Info :
Vial Number: 6

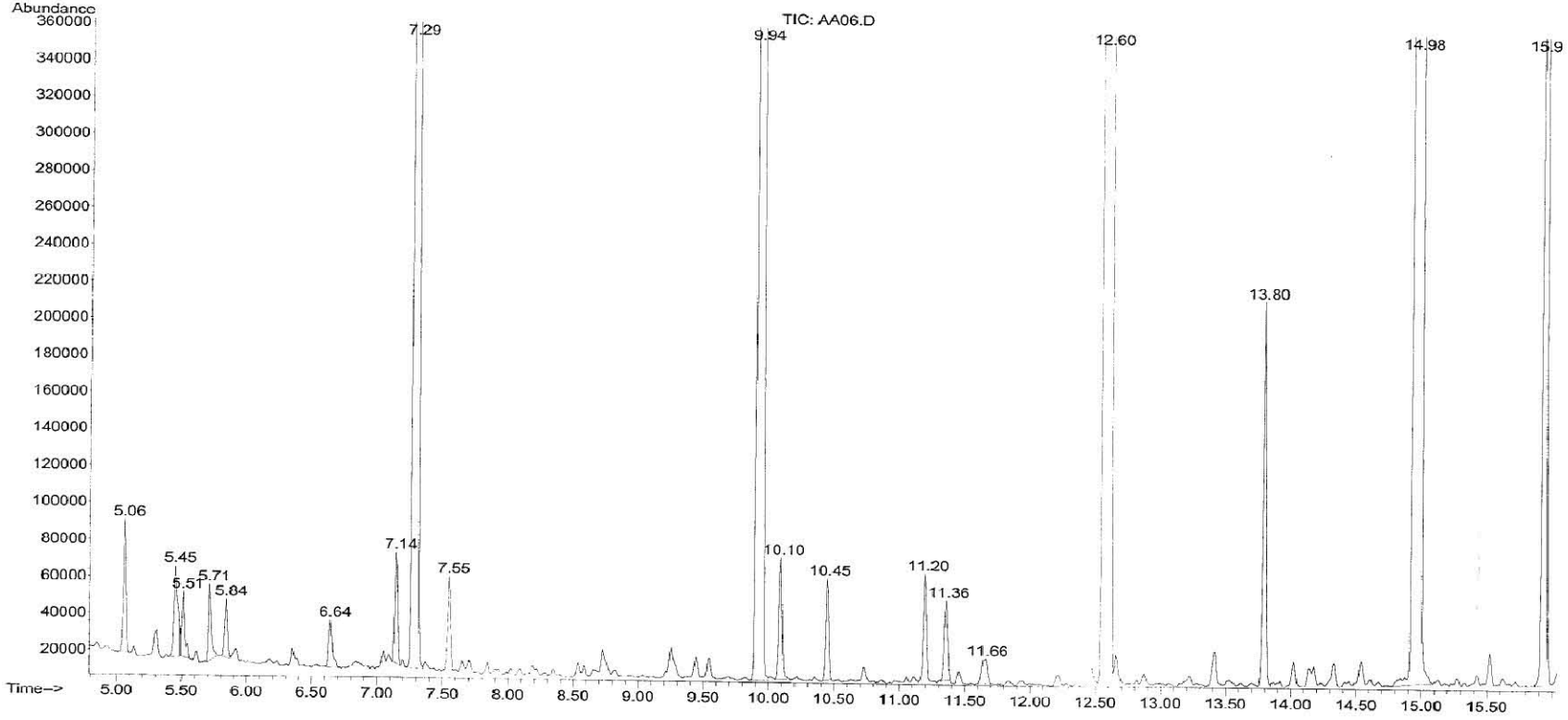

Figure 11 Ethyl acetate extract expanded scale (2)

```
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Operator    : [redacted]
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Instrument  :   Instrument #1
Sample Name: Ethyl acetate extract
Misc Info   :
Vial Number: 6
```

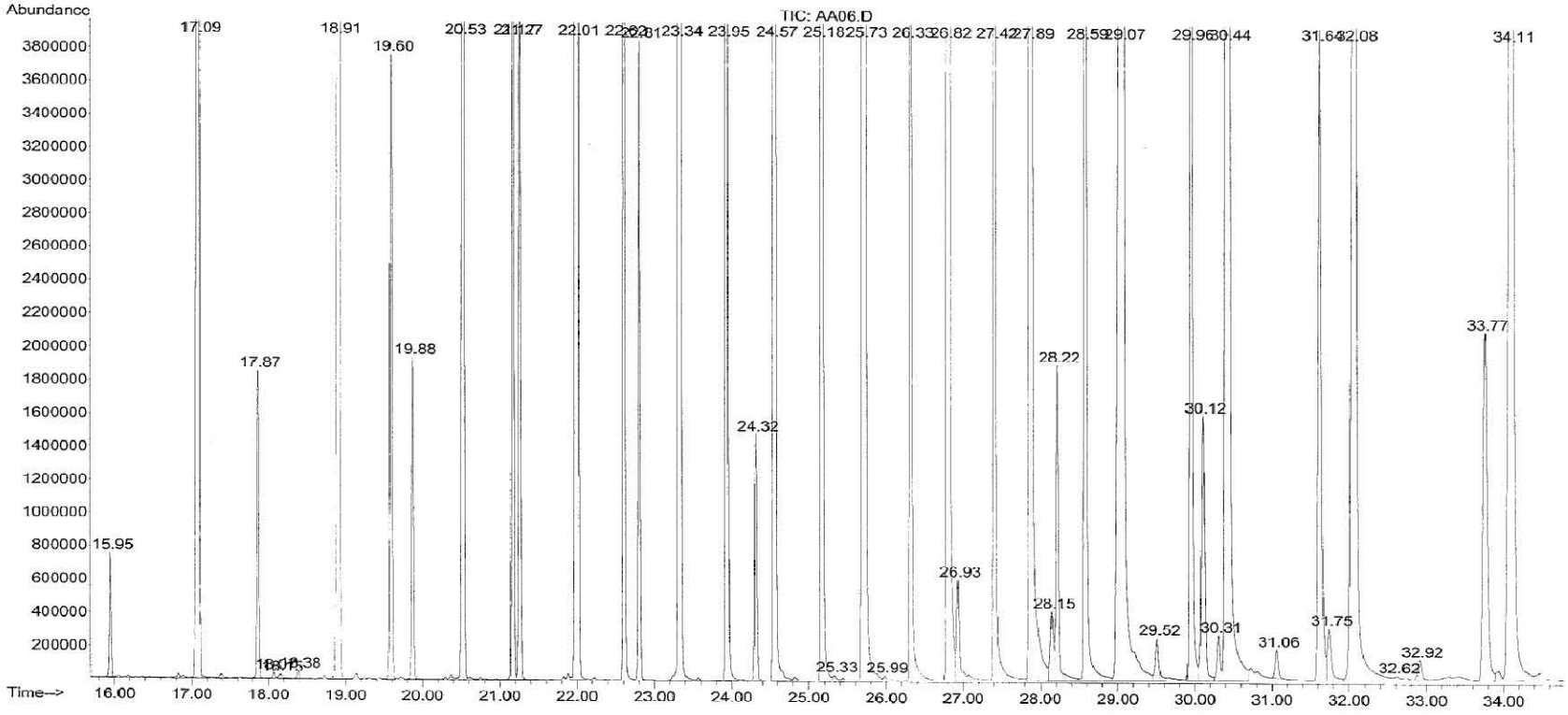

Figure 12 Ethyl acetate extract expanded scale (3)

```
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Acquired   : 27 Jul 2010  20:44     using AcqMethod 8232_400_SCAN.M
Instrument :   Instrument #1
Sample Name: Ethyl acetate extract
Misc Info  :
Vial Number: 6
```

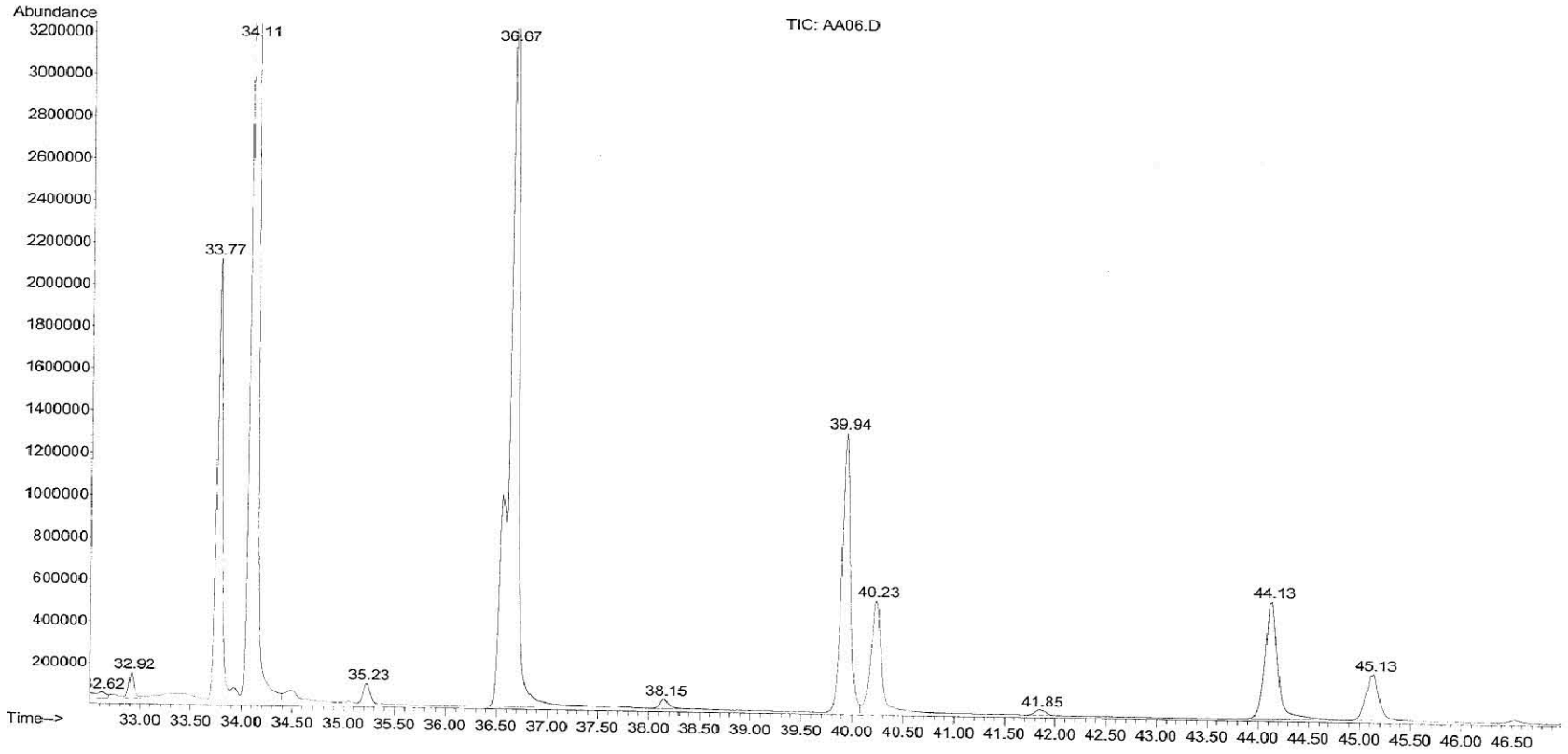

Figure 13 n-Heptane extract full scale

File :D:\HPChem_Data\8232-400\AA\AA08.D
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Instrument : Instrument #1
Sample Name: n-heptane extract
Misc Info :
Vial Number: 8

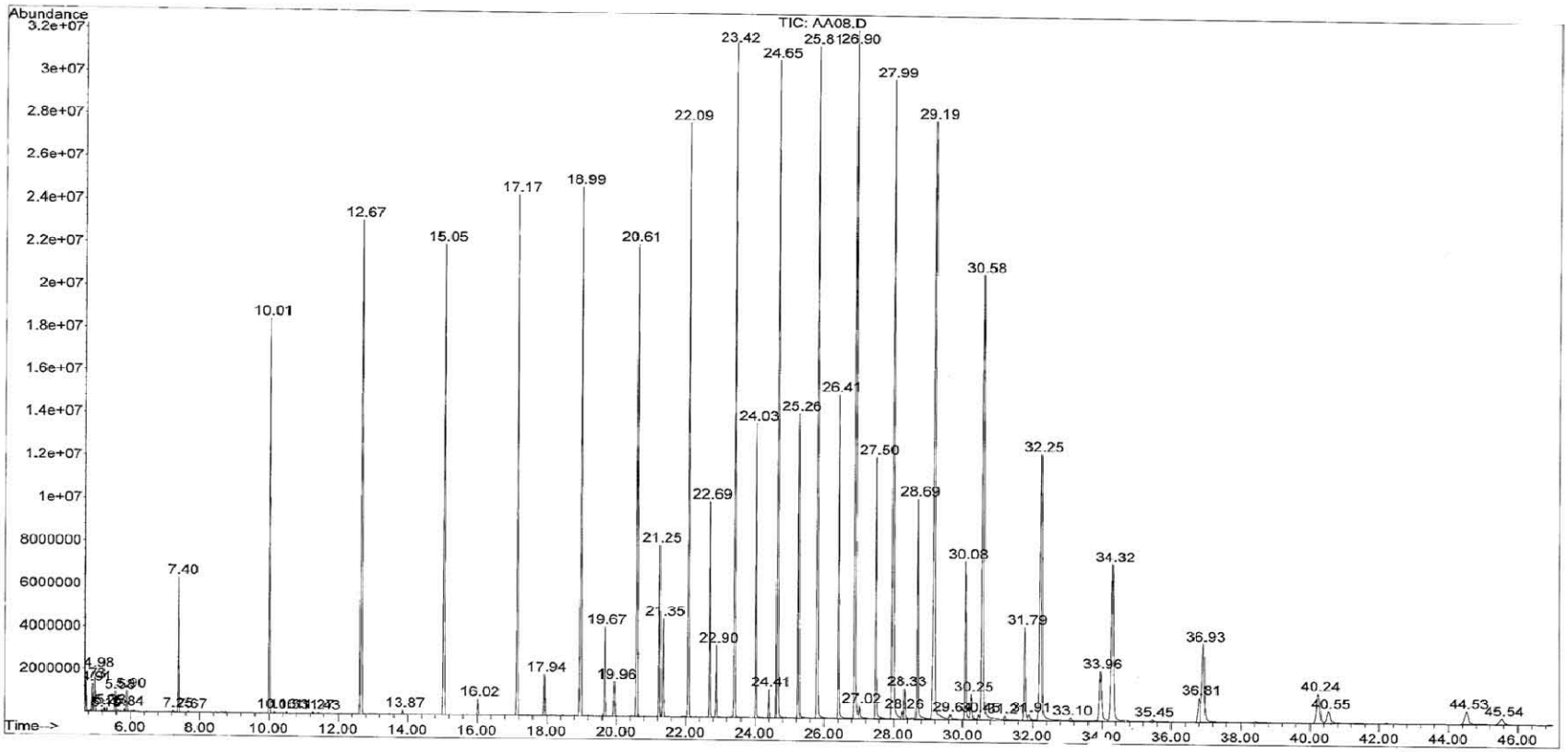

Figure 14 n-Heptane extract expanded scale (1)

```
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Operator   : [redacted]
Acquired   : 27 Jul 2010  22:40      using AcqMethod 8232_400_SCAN.M
Instrument :   Instrument #1
Sample Name: n-heptane extract
Misc Info  :
Vial Number: 8
```

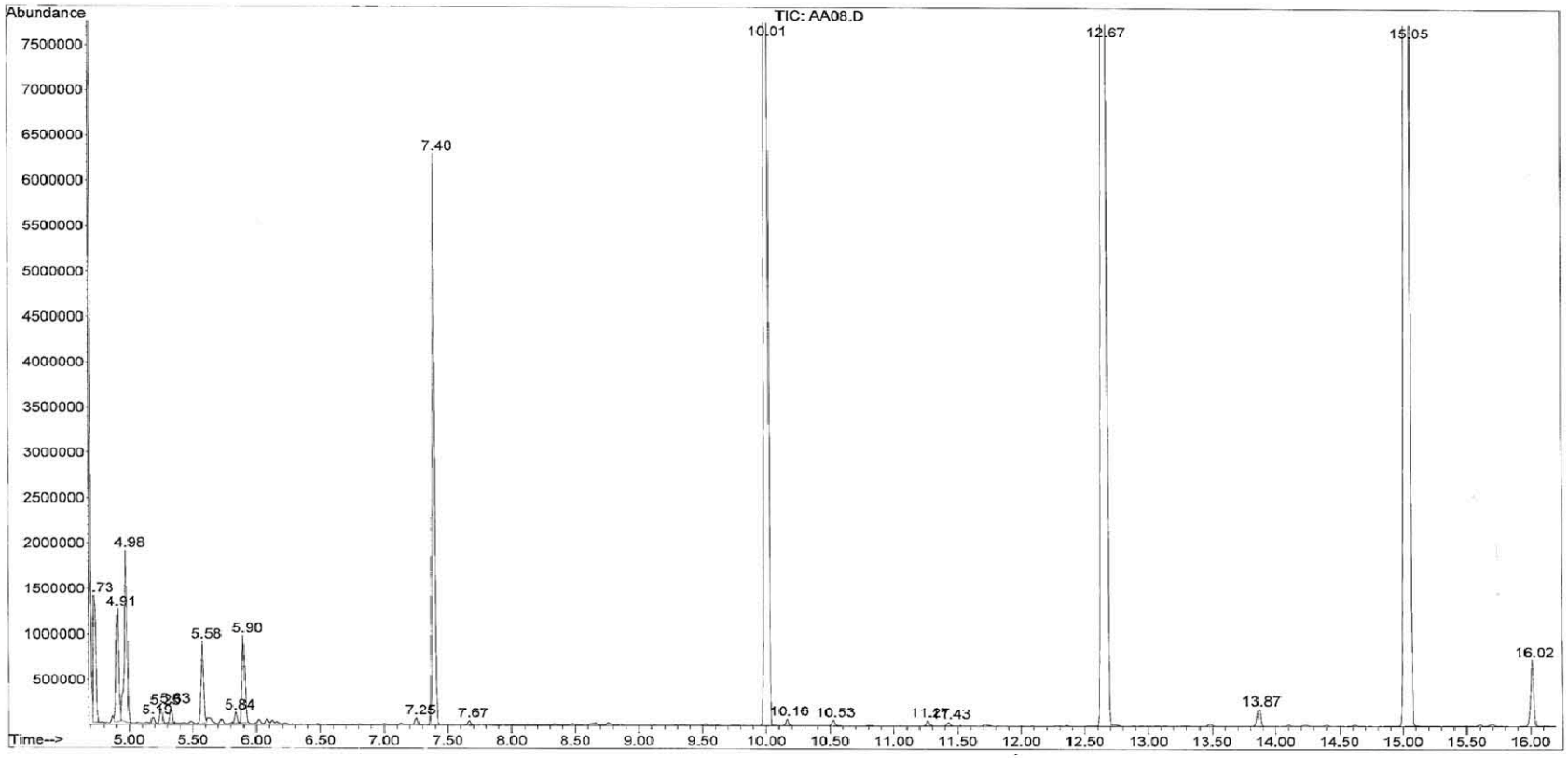

Figure 15 n-Heptane extract expanded scale (2)

```
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Operator    : [redacted]
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Instrument  :   Instrument #1
Sample Name: n-heptane extract
Misc Info   :
Vial Number: 8
```

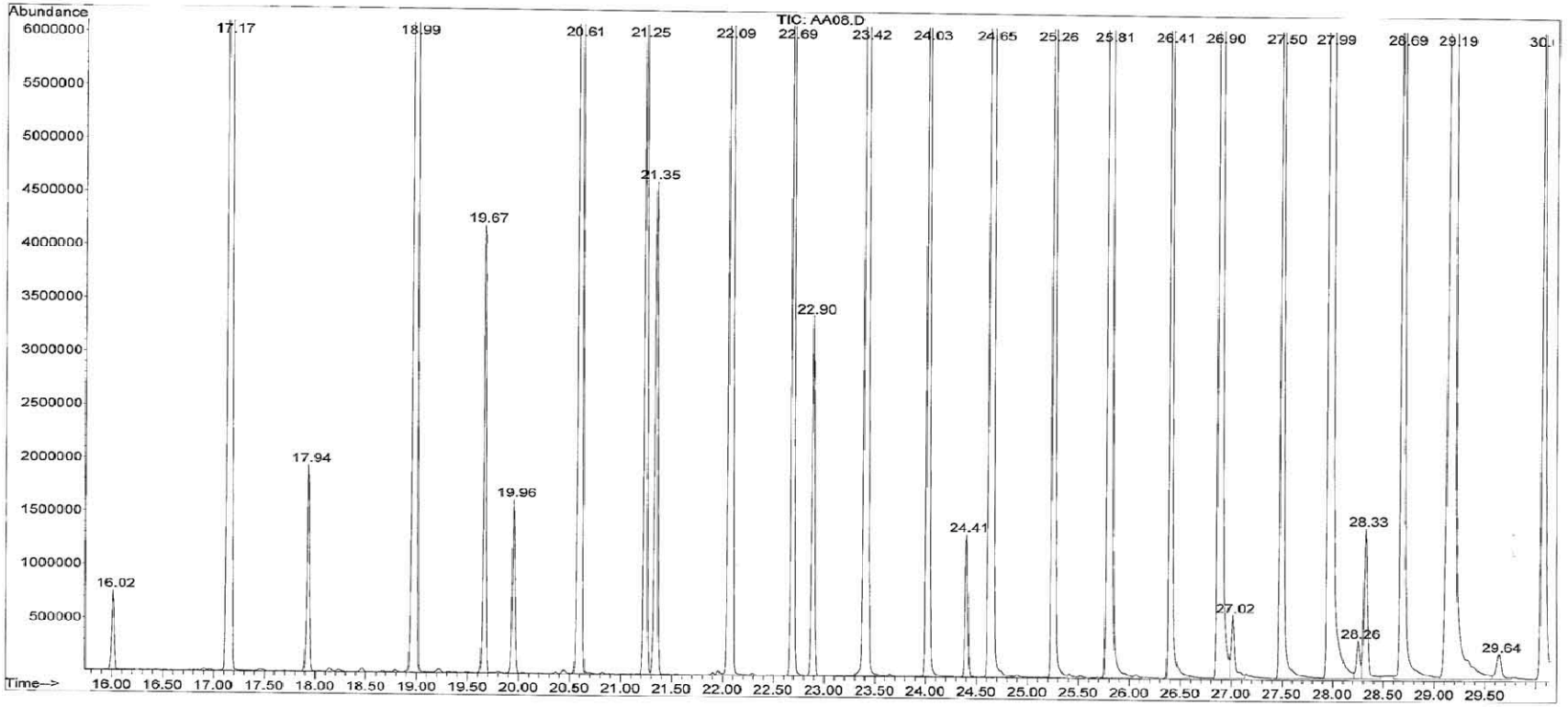

Figure 16 n-Heptane extract expanded scale (3)

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Operator : [redacted]
Acquired : 27 Jul 2010 22:40 using AcqMethod 8232_400_SCAN.M
Instrument : Instrument #1
Sample Name: n-heptane extract
Misc Info :
Vial Number: 8

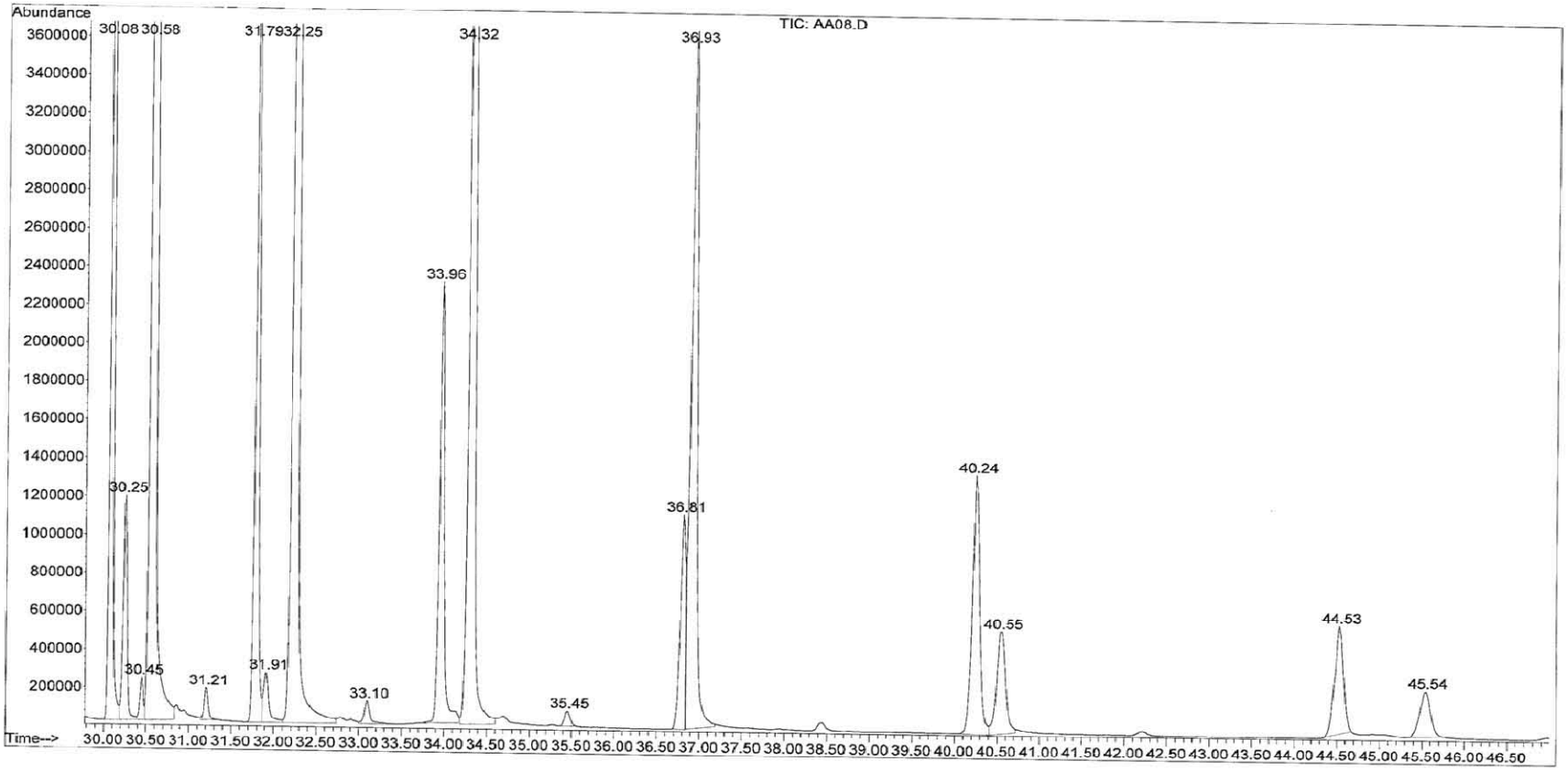

Figure 17 Toluene extract full scale

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Operator : [redacted]
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Instrument : Instrument #1
Sample Name: Toluene extract
Misc Info :
Vial Number: 10

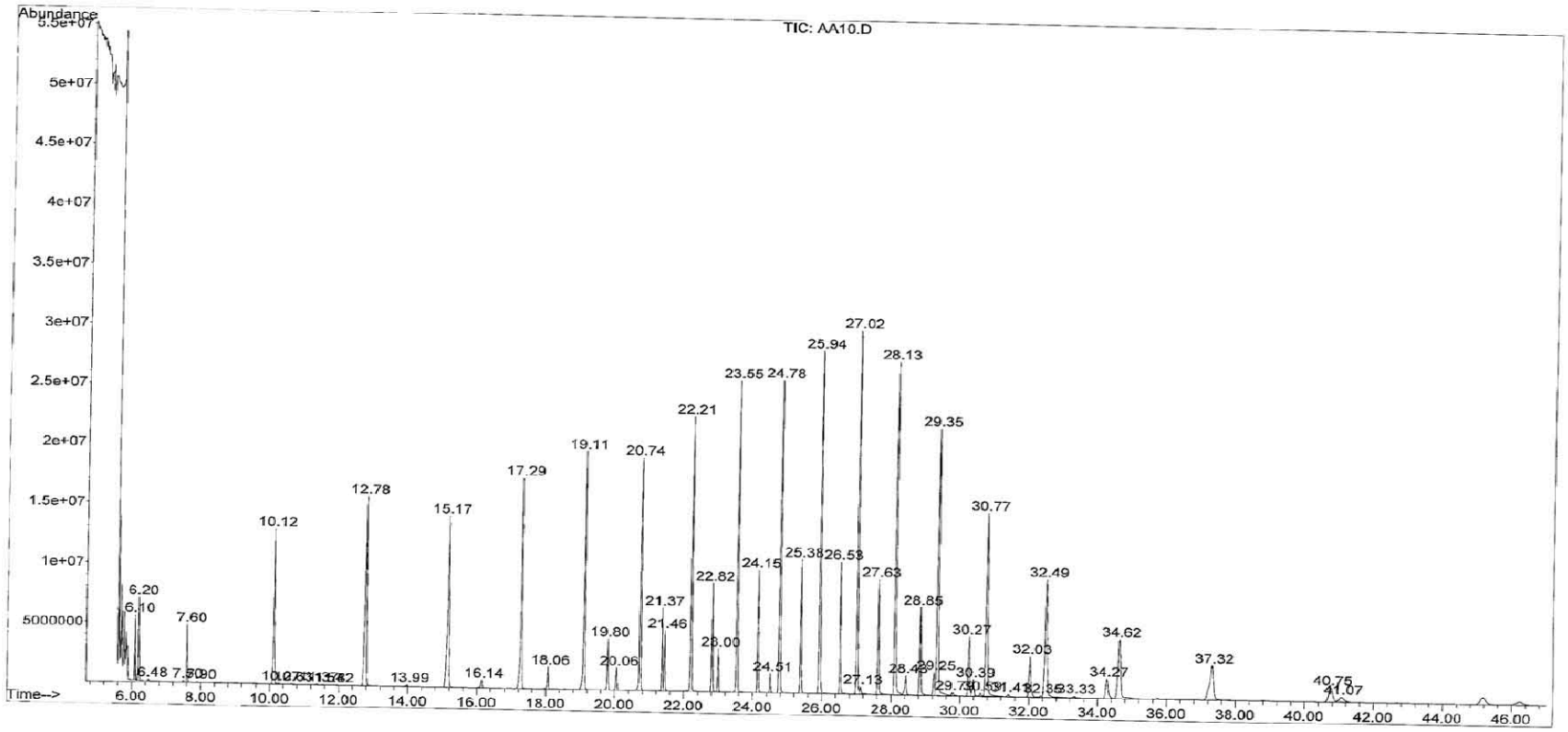

Figure 18 Toluene extract expanded scale (1)

```
File       :D:\HPChem Data\8232-400\AA\AA10.D
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Acquired   :  28 Jul 2010   00:35      using AcqMethod 8232_400_SCAN.M
Instrument :    Instrument #1
Sample Name: Toluene extract
Misc Info  :
Vial Number: 10
```

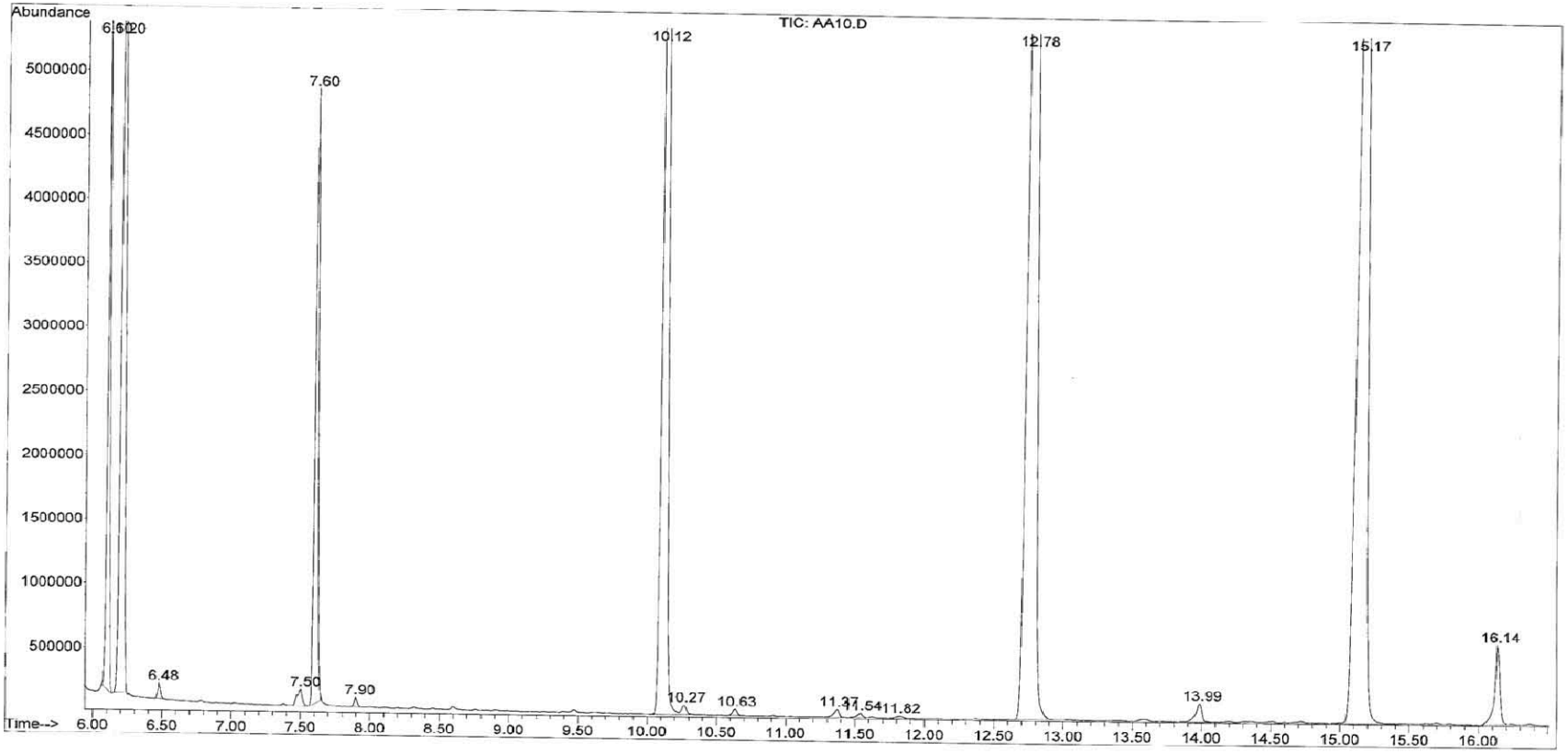

Figure 19 Toluene extract expanded scale (2)

File :D:\HPChem Data\8232-400\AA\AA10.D
Operator : [redacted]
Acquired : 28 Jul 2010 00:35 using AcqMethod 8232_400_SCAN.M
Instrument : Instrument #1
Sample Name: Toluene extract
Misc Info :
Vial Number: 10

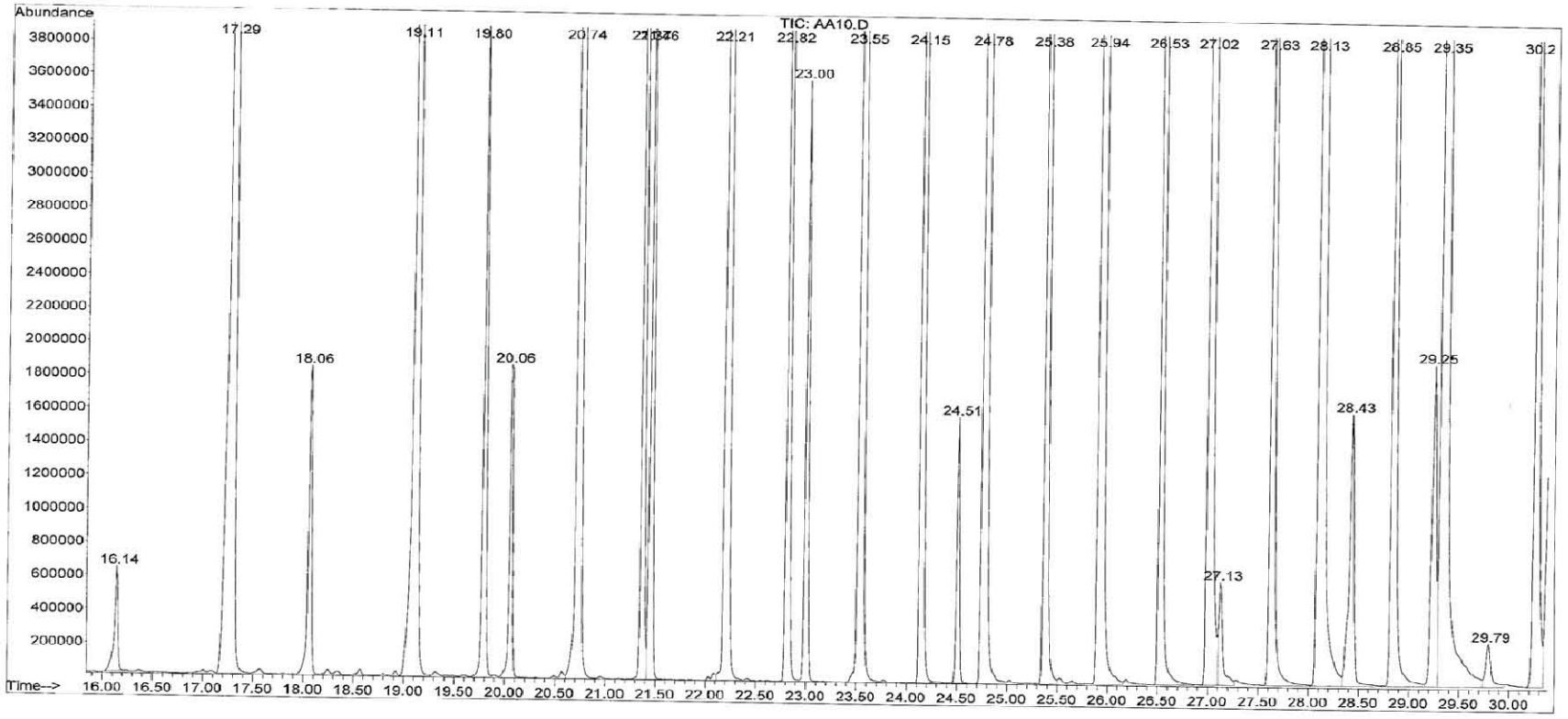

Figure 20 Toluene extract expanded scale (3)

```
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Operator   : [redacted]
Acquired   : 28 Jul 2010  00:35      using AcqMethod 8232_400_SCAN.M
Instrument :   Instrument #1
Sample Name: Toluene extract
Misc Info  :
Vial Number: 10
```

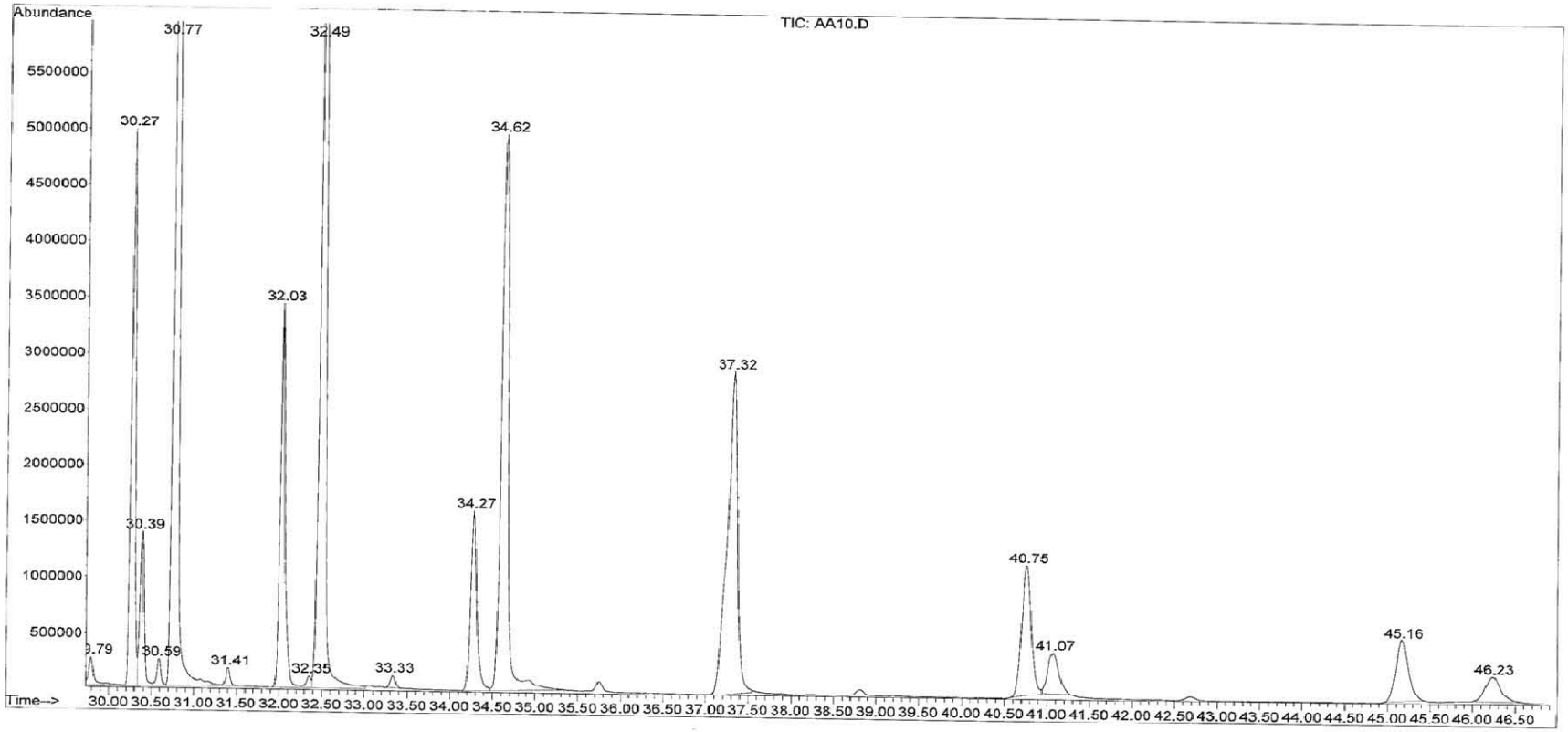

Figure 21 Head-space chromatograms full scale

```
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Operator   : [redacted]
Acquired   : 27 Jul 2010  23:52     using AcqMethod 8232400.M
Instrument :   Instrument #1
Sample Name: HP-52198-1 Prep 1
Misc Info  :
Vial Number: 7
```

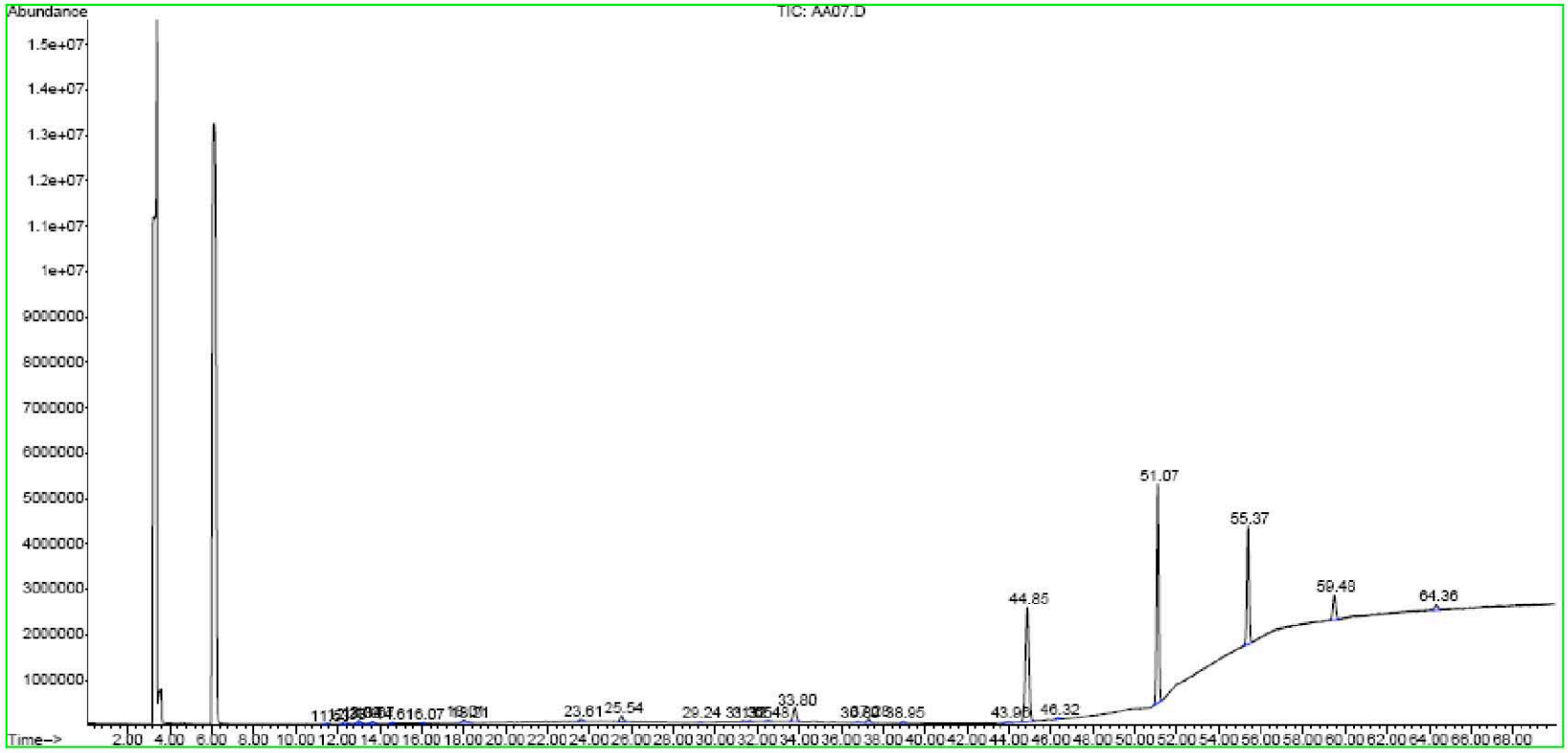

Figure 22 Head-space chromatogram expanded scale (1)

```
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Acquired    : 27 Jul 2010  23:52      using AcqMethod 8232400.M
Instrument  :   Instrument #1
Sample Name: HP-52198-1 Prep 1
Misc Info   :
Vial Number: 7
```

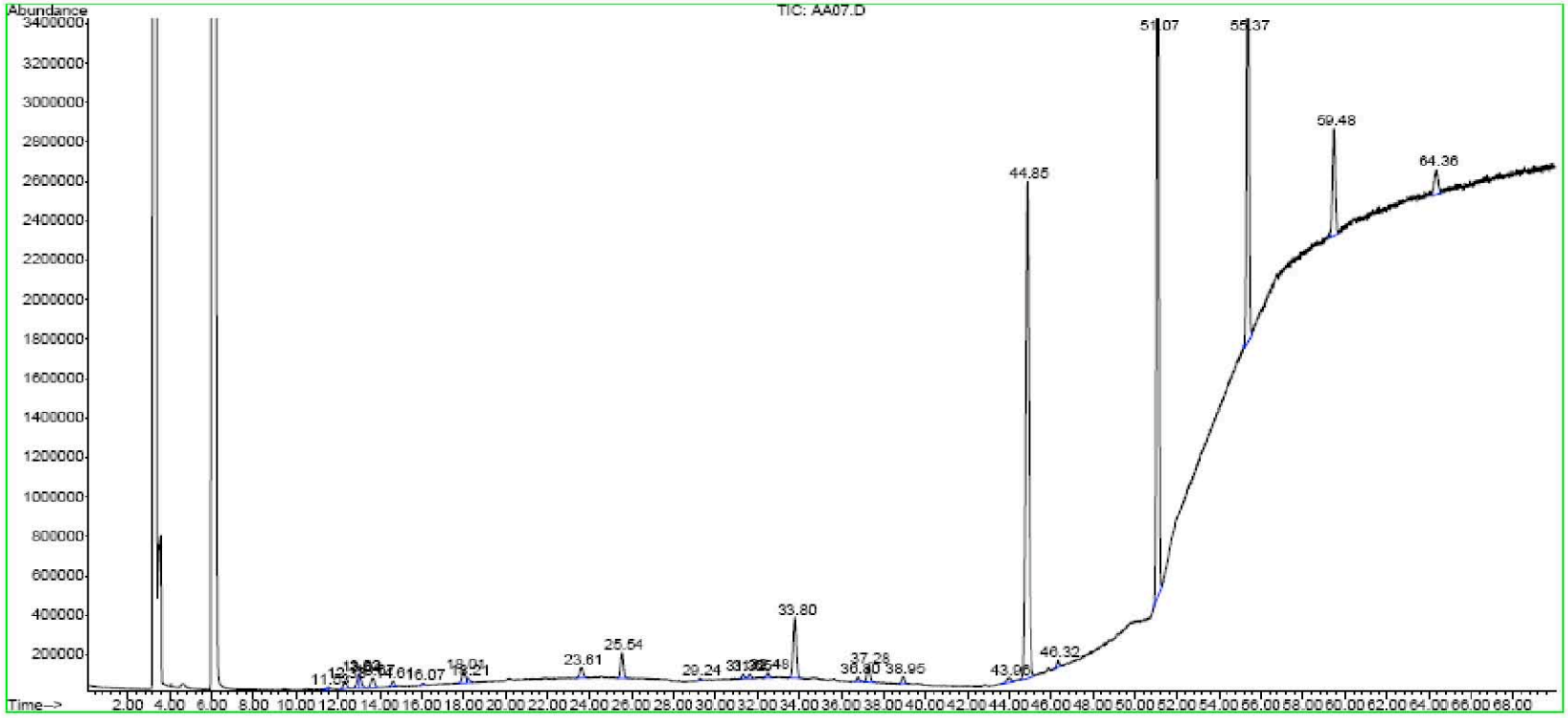

Figure 23 Head-space chromatogram expanded scale (2)

```
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Instrument :   Instrument #1
Sample Name: HP-52198-1 Prep 1
Misc Info  :
Vial Number: 7
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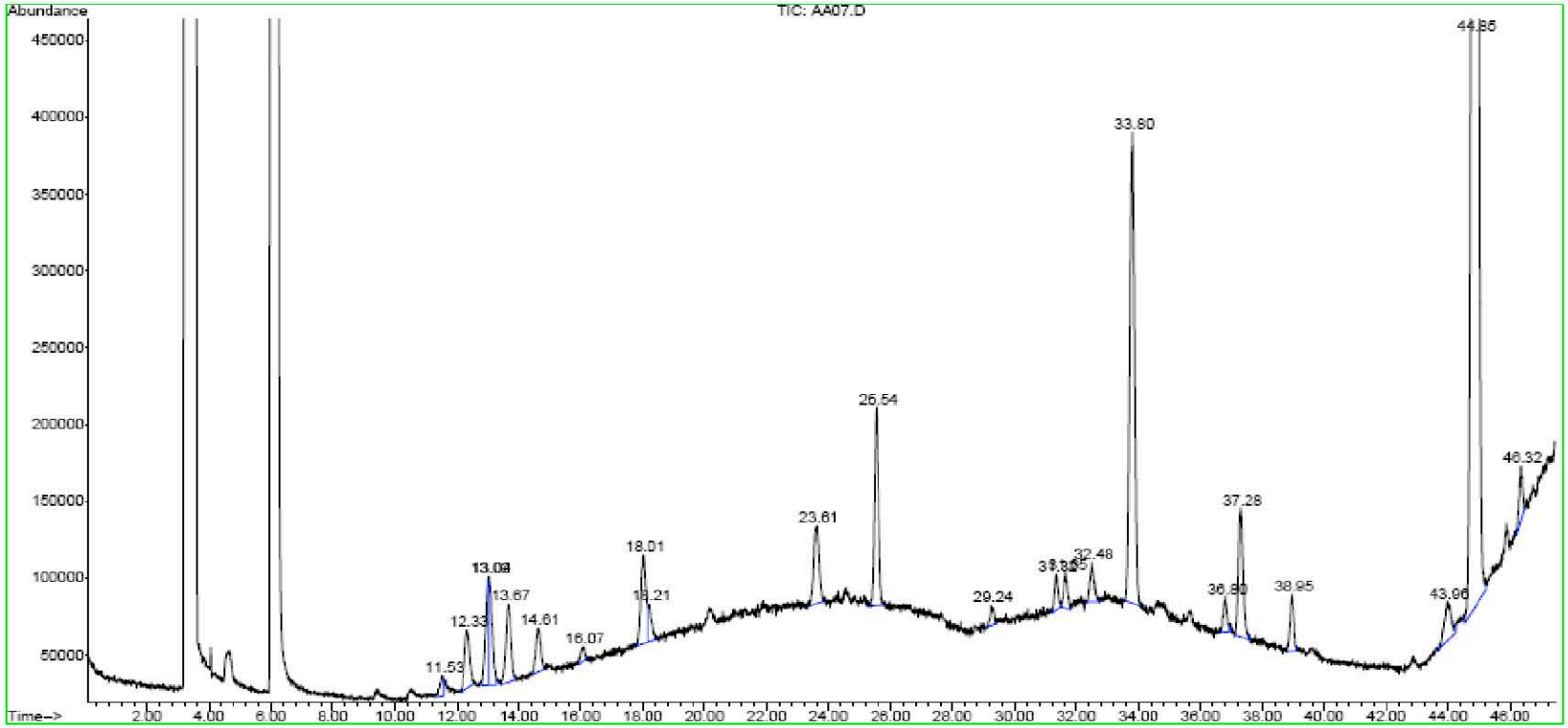

Figure 24 Head-space chromatogram expanded scale (3)

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Operator    : [redacted]
Acquired    : 27 Jul 2010  23:52      using AcqMethod 8232400.M
Instrument  :   Instrument #1
Sample Name: HP-52198-1 Prep 1
Misc Info   :
Vial Number: 7
```

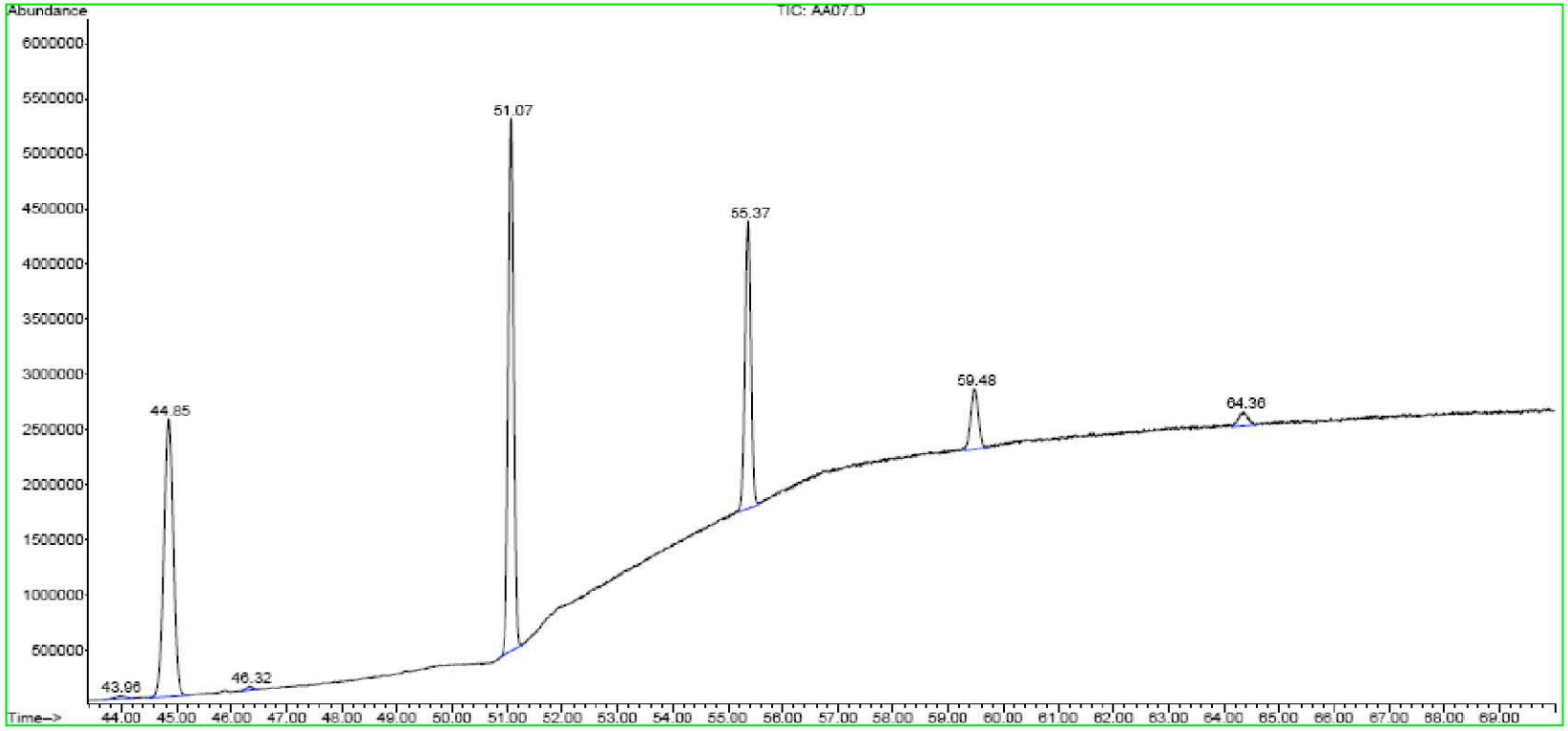

TABLES

Table 1 Chloroform extract

Peak number	RT (min)	Scan number	Peak ID (Wiley07/Nist5)	% Fit	Comment
1	6.063	133	Un-identified	-	m/z 83, 207, 151, 133, 179
2	**6.156**	**142**	**1,1,2,2-tetrachloroethane**	**95**	**-**
3	6.239	152	Un-identified	-	m/z 83, 207, 193, 281
4	7.047	230	1,1,3,3,5,5,7,7,Octamethyltetrasiloxane	64	-
5	7.193	243	1,1,3,3,5 Octamethylcyclotetrasiloxane	92	-
6	7.441	267	2,2,4,6,6-pentamethylheptane	59	-
7	9.877	502	Decamethyl-cyclopentasiloxane	91	-
8	10.042	517	1,1,3,3,5,5,7,7,9,9-decamethylpentasiloxane	94	-
9	10.395	552	Dodecamethyl-pentasiloxane	91	-
10	11.141	624	Un-identified	-	m/z 73, 327, 341, 207
11	11.307	640	Dodecamethylpentasiloxane	91	Fragmented oligomers
12	11.607	670	Un-identified	-	m/z 193, 207, 73, 327, 341
13	12.540	758	Dodecamethyl-cyclohexasiloxane	91	-
14	13.752	876	Tetradecamethyl-hexasiloxane	72	-
15	13.960	896	Un-identified	-	m/z 207, 105, 94, 44, 119
16	14.281	927	Un-identified	-	m/z 73, 207, 387, 44
17	14.488	947	Un-identified	-	m/z 207, 161, 91
18	14.923	988	Dodecamethyl-pentasiloxane	38	Fragmented oligomers
19	15.898	1083	Hexadecamethyl-heptasiloxane	80	-
20	17.037	1192	Tetracosamethylcyclododecasiloxane	64	-
21	17.815	1267	Un-identified	-	m/z 73, 221, 147, 207
22	18.861	1367	Tetradecamethyl-hexasiloxane	50	Fragmented oligomers

Peak number	RT (min)	Scan number	Peak ID (Wiley07/Nist5)	% Fit	Comment
23	19.545	1435	Hexadecamethyl-heptasiloxane	80	Fragmented oligomers
24	19.825	1463	Un-identified	-	m/z 327, 405, 156, 343
25	20.478	1524	Tetradecamethyl-hexasiloxane	43	Fragmented oligomers
26	21.121	1587	Hexadecamethyl-heptasiloxane	10	Fragmented oligomers
27	21.214	1596	Un-identified	-	m/z 135, 197, 479, 329, 73
28	21.950	1666	Un-identified	-	m/z 73, 147, 355, 221, 281
29	22.561	1726	Un-identified see Note 1	-	m/z 221, 73, 147, 295, 207
30	22.758	1745	Un-identified	-	m/z 135, 403, 197, 73
31	23.286	1797	Octadecamethylcyclononasiloxane	59	-
32	23.898	1854	Un-identified see Note 1	-	m/z, 221, 73, 147, 295, 207
33	24.271	1890	Bis[di(trimethylsiloxy)phenylsiloxy]trimethylsiloxane	47	-
34	24.509	1913	Tetradecamethyl-hexasiloxane	76	Fragmented oligomers
35	24.779	1940	Un-identified	-	m/z 207, 73, 147, 221, 281
36	25.131	1973	Tetradecamethyl-hexasiloxane	32	Fragmented oligomers
37	25.670	2025	Un-identified see Note 1	-	m/z, 221, 73, 147, 355, 281
38	26.281	2084	Un-identified see Note 1	-	m/z, 221, 73, 147, 295, 207
39	26.758	2131	Un-identified	-	m/z 355, 221, 147, 73, 429
40	26.882	2143	Un-identified see Note 2	-	m/z 135, 73, 147, 221
41	27.359	2190	Un-identified see Note 1	-	m/z, 221, 295, 147, 73, 281
42	27.825	2234	Un-identified	-	m/z 221, 355, 147, 73, 429
43	28.095	2258	Un-identified see Note 2	-	m/z 135, 73, 147, 221
44	28.157	2265	Un-identified	-	m/z 451, 218, 389, 373, 156
45	28.530	2302	Un-identified see Note 1	-	m/ z 221, 295, 147, 73, 369
46	28.996	2346	Un-identified see Note 1	-	m/z 221, 147, 73, 355, 281
47	29.442	2391	Un-identified see Note 2	-	m/z 135, 73, 147, 221, 207
48	29.888	2432	Un-identified see Note 1	-	m/z 221, 147, 73, 295, 281
49	30.033	2446	Un-identified see Note 3	-	m/z 197, 135, 259
50	30.230	2466	Un-identified see Note 3	-	m/z 135, 197, 73, 465, 259
51	30.354	2479	Un-identified see Note 1	-	m/z, 221, 73, 147, 355, 281

Peak number	RT (min)	Scan number	Peak ID (Wiley07/Nist5)	% Fit	Comment
52	30.976	2538	Un-identified see Note 2	-	m/z 135, 73, 147, 221
53	31.245	2569	Un-identified see Note 1	-	m/z 221, 147, 73, 207, 281
54	31.546	2593	Un-identified see Note 1	-	m/z 221, 147, 295, 73, 281
55	31.649	2603	Un-identified	-	m/z 135, 197, 73, 221
56	31.981	2634	Un-identified see Note 1	-	m/z 221, 147, 73, 355, 281
57	33.660	2795	Un-identified see Note 1	-	m/z 221, 147, 73, 295, 207
58	33.991	2826	Un-identified see Note 1	-	m/z 221, 147, 73, 281, 355
59	35.100	2936	Un-identified see Note 1		m/z 73, 135, 207, 147, 221
60	36.427	3062	Un-identified see Note 1	-	m/z 221, 147, 73, 295, 281
61	36.530	3074	Un-identified see Note 1	-	m/z 221, 147, 73, 355, 281
62	37.992	3215	Un-identified see Note 1	-	m/z 221, 147, 73, 207, 135
63	39.753	3384	Un-identified see Note 1	-	m/z 221, 147, 73, 281, 355
64	40.054	3413	Un-identified see Note 1	-	m/z 221, 147, 295, 73, 281
65	43.121	3707	Un-identified see Note 1	-	m/z 221, 207, 147, 281, 73
66	43.909	3785	Un-identified see Note 1	-	m/z 221, 147, 73, 281, 355
67	44.893	3878	Un-identified see Note 1	-	m/z 221, 147, 73, 295, 207

Note 1 Un-identified but likely to be polysiloxane oligomer fragments

Note 2 Un-identified but likely to be polysiloxane oligomer fragments from a different source than Note 1

Note 3 Closely related compounds

Peaks in **bold** text appear in the solvent blank

Table 2 Dichloromethane extract

Peak number	RT (min)	Scan number	Peak ID (Wiley07/Nist5)	% Fit	Comment
1	5.286	59	p-xylene	78	-
2	7.089	235	1,1,3,3,5,5-hexamethyl-trisiloxane	80	-
3	7.224	249	Octamethyl-cyclotetrasiloxane	91	-
4	9.918	504	Decamethyl-cyclopentasiloxane	91	-
5	10.084	521	1,1,3,3,5,5,7,7,9,9-decamethyl-pentasiloxane	91	-
6	10.436	556	Dodecamethyl-pentasiloxane	91	-
7	11.182	628	Un-identified	-	m/z 73, 327, 341, 401, 59
8	11.338	643	Dodecamethyl-pentasiloxane	87	Silicone oligomers fragment
9	11.649	672	Un-identified	-	m/z 73, 193, 327, 207, 415
10	12.581	763	Dodecamethyl-cyclohexasiloxane	91	-
11	13.783	879	Tetradecamethyl-hexasiloxane	35	-
12	14.965	992	Dodecamethyl-pentasiloxane	25	Silicone oligomers fragment
13	15.929	1086	Un-identified see Note 1	-	m/z 221, 73, 147, 207
14	17.079	1196	Tetracosamethylcyclo-dodecasiloxane	22	-
15	17.846	1271	Un-identified see Note 1	-	m/z 221, 73, 147, 207
16	18.903	1373	Octadecamethyl-cyclononasiloxane	45	-
17	19.576	1438	Hexadecamethyl-heptasiloxane	72	-
18	19.867	1466	Un-identified	-	m/z 327, 405, 156, 343, 253
19	20.519	1527	Tetradecamethyl-hexasiloxane	38	Silicone oligomers fragment
20	21.162	1588	Silicone polymer	53	-
21	21.255	1599	Un-identified see Note 2	-	m/z 135, 197, 73, 479, 329
22	21.991	1670	Tetracosamethylcyclo-dodecasiloxane	58	Silicone oligomers fragment
23	22.602	1729	Un-identified see Note 1	-	m/z 221, 73, 147, 295, 207
24	22.799	1748	Un-identified see Note 2	-	m/z 135, 197, 73, 403, 341
25	23.328	1798	Tetradecamethyl-hexasiloxane	59	Silicone oligomers fragment
26	23.929	1858	Un-identified see Note 1	-	m/z 221, 73, 147, 295, 281

Peak number	RT (min)	Scan number	Peak ID (Wiley07/Nist5)	% Fit	Comment
27	24.302	1894	Un-identified see Note 2	-	m/z 135, 73, 197, 209, 327
28	24.551	1918	Octadecamethyl-cyclononasiloxane	59	Silicone oligomers fragment
29	25.162	1977	Tetradecamethyl-hexasiloxane	25	Silicone oligomers fragment
30	25.711	2030	Octadecamethyl-cyclononasiloxane	47	Silicone oligomers fragment
31	26.312	2088	Hexadecamethyl-heptasiloxane	33	Silicone oligomers fragment
32	26.799	2133	Octadecamethyl-cyclononasiloxane	83	Silicone oligomers fragment
33	26.913	2146	Nonamethylphenyl-cyclopentasiloxane	38	-
34	27.400	2193	Hexadecamethyl-heptasiloxane	33	Silicone oligomers fragment
35	27.877	2237	Octadecamethyl-cyclononasiloxane	80	Silicone oligomers fragment
36	28.136	2263	Un-identified see Note 2	-	m/z 135, 73, 147, 221
37	28.198	2270	Un-identified	-	m/z 451, 218, 389, 373, 156
38	28.571	2306	Hexadecamethyl-heptasiloxane	25	Silicone oligomers fragment
39	29.059	2351	Tetradecamethyl-hexasiloxane	43	Silicone oligomers fragment
40	29.494	2395	Un-identified see Note 2	-	m/z 135, 73, 147, 221, 355
41	29.939	2437	Un-identified see Note 1	-	m/z 221, 147, 73, 295
42	30.095	2453	Un-identified	-	m/z 197, 135, 259, 391
43	30.292	2471	Un-identified see Note 2	-	m/z 135, 197, 73, 465, 259
44	30.416	2483	Octadecamethyl-cyclononasiloxane	72	Silicone oligomers fragment
45	31.038	2544	Un-identified see Note 2	-	m/z 135, 73, 147, 221, 281
46	31.608	2599	Hexadecamethyl-heptasiloxane	33	Silicone oligomers fragment
47	31.722	2610	Un-identified	-	m/z 135, 197, 73, 465
48	32.053	2642	Tetracosamethylcyclo-dodecasiloxane	72	Silicone oligomers fragment
49	32.883	2722	Un-identified see Note 2	-	m/z 135, 73, 147, 221, 207
50	33.732	2805	Hexadecamethyl-heptasiloxane	53	Silicone oligomers fragment
51	34.085	2835	Octadecamethyl-cyclononasiloxane	86	Silicone oligomers fragment
52	35.183	2945	Un-identified see Note 2	-	m/z 135, 73, 147, 221, 207
53	36.520	3071	Hexadecamethyl-heptasiloxane	59	Silicone oligomers fragment
54	36.624	3083	Octadecamethyl-cyclononasiloxane	64	Silicone oligomers fragment
55	39.888	3397	Octadecamethyl-cyclononasiloxane	80	Silicone oligomers fragment

Peak number	RT (min)	Scan number	Peak ID (Wiley07/Nist5)	% Fit	Comment
56	40.188	3426	Hexadecamethyl-heptasiloxane	53	Silicone oligomers fragment
57	44.054	3799	Octadecamethyl-cyclononasiloxane	86	Silicone oligomers fragment
58	45.028	3895	Hexadecamethyl-heptasiloxane	45	Silicone oligomers fragment

Note 1 Un-identified but likely to be polysiloxane oligomer fragments
Note 2 Un-identified compounds but related fragments

Peaks in **bold** text appear in the solvent blank

Table 3 Ethyl acetate extract

Peak number	RT (min)	Scan number	Peak ID (Wiley07/Nist5)	% Fit	Comment
1	**5.058**	**37**	**Ethyl 2-methyl butyrate**	**94**	**-**
2	5.452	75	m-xylene	94	-
3	**5.514**	**81**	**Iso-amylacetate**	**80**	**-**
4	**5.711**	**100**	**Un-identified**	**-**	**m/z 133, 151, 43, 207**
5	5.845	113	p-xylene	95	-
6	6.643	191	Un-identified	-	m/z 193, 209, 43, 97
7	7.141	238	1,1,3,3,5,5,7,7-octamethyl-tetrasiloxane	55	-
8	7.286	251	1,1,3,3,5,5,7,7-octamethyl-cyclotetrasiloxane	91	-
9	7.545	277	2,2,4,6,6-pentamethylheptane	59	-
10	9.939	507	Decamethyl-cyclopentasiloxane	91	-
11	10.094	522	1,1,3,3,5,5,7,7,9,9-decamethyl-pentasiloxane	91	-
12	10.447	557	Dodecamethyl-pentasiloxane	91	-
13	11.203	629	Un-identified	-	m/z 73, 327, 341, 59
14	11.359	645	Dodecamethyl-pentasiloxane	94	Silicone oligomers fragment
15	11.659	672	Un-identified	-	m/z 73, 327, 415, 207, 43
16	12.602	763	Dodecamethyl-cyclohexasiloxane	91	-
17	13.804	880	Tetradecamethyl-hexasiloxane	58	-
18	14.975	992	Dodecamethyl-pentasiloxane	38	Silicone oligomers fragment
19	15.949	1088	Hexadecamethyl-heptasiloxane	56	-
20	17.089	1197	Tetracosamethyl-cyclododecasiloxane	10	-
21	17.867	1272	Un-identified	-	m/z 73, 221, 147, 207, 295
22	18.063	1292	n-heptadecane	86	-
23	18.157	1301	Un-identified	-	m/z 207, 129, 222, 73, 91
24	18.385	1323	2,3-dihydro-1,1,3-trimethyl-3-phenyl-1H-Indene	81	CAS 3910-35-8
25	18.913	1373	Octadecamethyl-cyclononasiloxane	87	-

Peak number	RT (min)	Scan number	Peak ID (Wiley07/Nist5)	% Fit	Comment
26	19.597	1439	Hexadecamethyl-heptasiloxane	32	Silicone oligomers fragment
27	19.877	1467	Un-identified	-	m/z 327, 405, 156, 253, 343
28	20.530	1530	Tetradecamethyl-hexasiloxane	43	Silicone oligomers fragment
29	21.172	1592	Hexadecamethyl-heptasiloxane	10	Silicone oligomers fragment
30	21.266	1601	Un-identified Note 1	-	m/z 135, 197, 479, 73, 329
31	22.001	1672	Tetracosamethyl-cyclododecasiloxane	58	Silicone oligomers fragment
32	22.613	1731	Hexadecamethyl-heptasiloxane	59	Silicone oligomers fragment
33	22.810	1751	Un-identified Note 1	-	m/z 135,403, 197, 341, 73
34	23.338	1800	Tetracosamethyl-cyclododecasiloxane	25	Silicone oligomers fragment
35	23.950	1860	Hexadecamethyl-heptasiloxane	10	Silicone oligomers fragment
36	24.323	1895	Bis[di(trimethylsiloxy)phenylsiloxy]-trimethylsiloxane	64	-
37	24.571	1919	Octadecamethyl-cyclononasiloxane	53	Silicone oligomers fragment
38	25.183	1978	Hexadecamethyl-heptasiloxane	53	Silicone oligomers fragment
39	25.338	1994	Silicate ion tetramer	53	-
40	25.732	2031	Tetracosamethyl-cyclododecasiloxane	64	Silicone oligomers fragment
41	25.981	2056	Tetradecamethyl-hexasiloxane	43	-
42	26.333	2089	Un-identified	-	m/z 221, 147, 73, 295, 281
43	26.820	2136	Tetracosamethyl-cyclododecasiloxane	38	Silicone oligomers fragment
44	26.934	2148	Bis[di(trimethylsiloxy)phenylsiloxy]-trimethylsiloxane	38	Silicone oligomers fragment
45	27.411	2194	Hexadecamethyl-heptasiloxane	42	Silicone oligomers fragment
46	27.888	2238	Octadecamethyl-cyclononasiloxane	91	Silicone oligomers fragment
47	28.157	2265	Un-identified Note 1	-	m/z 135, 73, 147, 221, 281
48	28.219	2270	Un-identified	-	m/z 218, 451, 389, 156, 373
49	28.592	2308	Hexadecamethyl-heptasiloxane	16	Silicone oligomers fragment
50	29.069	2354	Tetracosamethyl-cyclododecasiloxane	49	Silicone oligomers fragment
51	29.515	2397	Un-identified Note 1	-	m/z 135, 73, 147, 221, 281
52	29.960	2440	Hexadecamethyl-heptasiloxane	25	Silicone oligomers fragment
53	30.116	2455	Un-identified	-	m/z 197, 135, 259, 313, 391
54	30.313	2474	Un-identified	-	m/z 135, 197, 73, 465

Peak number	RT (min)	Scan number	Peak ID (Wiley07/Nist5)	% Fit	Comment
55	30.437	2485	Octadecamethyl-cyclononasiloxane	72	Silicone oligomers fragment
56	31.059	2545	Un-identified	-	m/z 135, 73, 147, 221, 207
57	31.639	2601	Hexadecamethyl-heptasiloxane	33	Silicone oligomers fragment
58	31.753	2612	Un-identified Note 1	-	m/z 135, 197, 73, 465
59	32.085	2641	Octadecamethyl-cyclononasiloxane	91	Silicone oligomers fragment
60	32.623	2696	Octadecamethyl-cyclononasiloxane	45	Silicone oligomers fragment
61	32.914	2725	Octadecamethyl-cyclononasiloxane	45	Silicone oligomers fragment
62	33.774	2808	Hexadecamethyl-heptasiloxane	33	Silicone oligomers fragment
63	34.116	2842	Octadecamethyl-cyclononasiloxane	86	Silicone oligomers fragment
64	35.225	2948	Un-identified Note 1	-	m/z 135, 73, 147, 207, 221
65	36.665	3088	Tetracosamethyl-cyclododecasiloxane	64	Silicone oligomers fragment
66	38.147	3230	Un-identified Note 1	-	m/z 135, 73, 207, 147, 221
67	39.940	3403	Octadecamethyl-cyclononasiloxane	90	Silicone oligomers fragment
68	40.230	3431	Hexadecamethyl-heptasiloxane	53	Silicone oligomers fragment
69	41.847	3586	Un-identified	-	m/z 207, 73, 135, 147, 281
70	44.137	3807	Tetracosamethyl-cyclododecasiloxane	72	Silicone oligomers fragment
71	45.132	3903	Hexadecamethyl-heptasiloxane	59	Silicone oligomers fragment

Note 1 Un-identified compounds but related fragments

Peaks in **bold** text appear in the solvent blank

Table 4 n-heptane extract

Peak number	RT (min)	Scan number	Peak ID (Wiley07/Nist5)	% Fit	Comment
1	4.726	6	Hexamethyl-cyclotrisiloxane	90	-
2	**4.913**	**23**	**Un-identified**	**-**	**m/z 43, 55, 73, 85**
3	**4.975**	**29**	**Un-identified**	**-**	**m/z 43, 55, 73, 85**
4	5.182	50	Tetrahydro-2H-Pyran-2-methanol	64	-
5	**5.255**	**56**	**2-ethyl-3-propyloxirane**	**53**	**-**
6	**5.327**	**63**	**Cis-2,3-epoxyheptane**	**38**	**-**
7	**5.576**	**87**	**Tetrahydro[2,2']bifuranyl-5-one**	**78**	**-**
8	**5.835**	**112**	**3-heptanone**	**90**	**-**
9	**5.897**	**118**	**2-heptanone**	**91**	**-**
10	7.255	249	1,1,3,3,5,5,7,7-octamethyl-tetrasiloxane	93	-
11	7.400	262	Octamethyl-cyclotetrasiloxane	91	-
12	7.669	288	2,2,4,6,6-pentamethylheptane	72	-
13	10.011	514	Decamethyl-cyclopentasiloxane	91	-
14	10.167	530	Un-identified	-	m/z 267, 281, 73, 133, 207
15	10.529	565	Dodecamethyl-pentasiloxane	91	-
16	11.265	636	Un-identified	-	m/z 73, 327, 341, 401
17	11.431	652	Dodecamethyl-pentasiloxane	94	Silicone oligomers fragment
18	12.675	770	Dodecamethyl-cyclohexasiloxane	91	-
19	13.877	888	Tetradecamethyl-hexasiloxane	80	-
20	15.048	999	Dodecamethyl-pentasiloxane	40	Silicone oligomers fragment
21	16.022	1094	Unidentified	-	m/z 221, 73, 147, 207
22	17.162	1204	Tetracosamethyl-cyclododecasiloxane	32	-
23	17.939	1279	Un-identified	-	m/z 73, 221, 147, 207
24	18.986	1380	Octadecamethyl-cyclononasiloxane	83	-
25	19.670	1446	Hexadecamethyl-heptasiloxane	64	-
26	19.960	1474	Un-identified	-	m/z 327, 405, 156, 253, 343
27	20.613	1537	Octadecamethyl-cyclononasiloxane	46	-

Peak number	RT (min)	Scan number	Peak ID (Wiley07/Nist5)	% Fit	Comment
28	21.245	1599	Un-identified	-	m/z 221, 73, 147,295, 281
29	21.348	1608	Un-identified Note 1	-	m/z 135, 197, 73, 329
30	22.084	1680	Tetracosamethyl-cyclododecasiloxane	49	Silicone oligomers fragment
31	22.696	1736	Tetracosamethyl-cyclododecasiloxane	46	Silicone oligomers fragment
32	22.893	1758	Un-identified Note 1	-	m/z 135, 197, 403, 73
33	23.421	1807	Tetradecamethyl-hexasiloxane	62	Silicone oligomers fragment
34	24.022	1869	Hexadecamethyl-heptasiloxane	42	Silicone oligomers fragment
35	24.406	1904	Bis[di(trimethylsiloxy)phenylsiloxy]-trimethylsiloxane	42	-
36	24.654	1927	Octadecamethyl-cyclononasiloxane	53	Silicone oligomers fragment
37	25.266	1985	Un-identified	-	m/z 221, 73, 147, 295, 207
38	25.815	2039	Tetracosamethyl-cyclododecasiloxane	64	Silicone oligomers fragment
39	26.406	2098	Hexadecamethyl-heptasiloxane	38	Silicone oligomers fragment
40	26.903	2143	Tetracosamethyl-cyclododecasiloxane	49	Silicone oligomers fragment
41	27.017	2156	Un-identified Note 1	-	m/z 135, 73, 147, 221, 209
42	27.504	2203	Hexadecamethyl-heptasiloxane	25	Silicone oligomers fragment
43	27.991	2246	Tetradecamethyl-hexasiloxane	87	Silicone oligomers fragment
44	28.261	2275	Un-identified Note 1	-	m/z 135, 73, 147, 221, 209
45	28.333	2282	Un-identified	-	m/z 451, 218, 389, 373, 156
46	28.696	2318	Hexadecamethyl-heptasiloxane	25	Silicone oligomers fragment
47	29.183	2365	Un-identified	-	m/z 221, 355, 147, 281, 429
48	29.639	2409	Un-identified Note 1	-	m/z 135, 73, 147, 221, 281
49	30.084	2452	Hexadecamethyl-heptasiloxane	25	Silicone oligomers fragment
50	30.250	2468	Un-identified	-	m/z 197, 135, 259
51	30.447	2487	Un-identified Note 1	-	m/z 135, 197, 73, 465
52	30.572	2499	Hexadecamethyl-heptasiloxane	22	Silicone oligomers fragment
53	31.214	2561	Octadecamethyl-cyclononasiloxane	43	Silicone oligomers fragment
54	31.794	2616	Hexadecamethyl-heptasiloxane	40	Silicone oligomers fragment
55	31.919	2628	Un-identified Note 1	-	m/z 135, 197, 73, 221, 465
56	32.250	2661	Octadecamethyl-cyclononasiloxane	87	Silicone oligomers fragment

Peak number	RT (min)	Scan number	Peak ID (Wiley07/Nist5)	% Fit	Comment
57	33.100	2743	Un-identified Note 1	-	m/z 135, 73, 147, 207, 221
58	33.960	2825	Hexadecamethyl-heptasiloxane	40	Silicone oligomers fragment
59	34.313	2860	Octadecamethyl-cyclononasiloxane	72	Silicone oligomers fragment
60	35.453	2970	Un-identified Note 1	-	m/z 135, 73, 147, 207, 221
61	36.810	3100	Hexadecamethyl-heptasiloxane	53	Silicone oligomers fragment
62	36.934	3111	Octadecamethyl-cyclononasiloxane	86	Silicone oligomers fragment
63	40.240	3433	Octadecamethyl-cyclononasiloxane	90	Silicone oligomers fragment
64	40.551	3461	Hexadecamethyl-heptasiloxane	28	Silicone oligomers fragment
65	44.531	3846	Tetracosamethyl-cyclododecasiloxane	22	Silicone oligomers fragment
66	45.546	3943	Hexadecamethyl-heptasiloxane	39	Silicone oligomers fragment

Note 1 Un-identified compounds but related fragments

Peaks in **bold** text appear in the solvent blank

Table 5 Toluene extract

Peak number	RT (min)	Scan number	Peak ID (Wiley07/Nist5)	% Fit	Comment
1	**6.104**	**138**	**Ethylbenzene**	**95**	**-**
2	**6.198**	**147**	**1,3-dimethylbenzene**	**97**	**-**
3	**6.477**	**174**	**o-xylene**	**53**	**-**
4	7.503	270	Un-identified	-	m/z 193, 207, 91, 73, 267
5	7.607	283	Octamethyl-cyclotetrasiloxane	91	-
6	7.897	311	2,2,4,6,6-pentamethylheptane	53	-
7	10.125	524	Decamethyl-cyclopentasiloxane	91	-
8	10.270	540	Un-identified	-	m/z 267, 281, 73, 91, 133
9	10.633	575	Dodecamethyl-pentasiloxane	90	-
10	11.369	646	Un-identified	-	m/z 327, 73, 91, 341, 401
11	11.535	662	Dodecamethyl-pentasiloxane	87	-
12	11.814	690	Un-identified	-	m/z 91, 327, 73, 193, 207
13	12.778	781	Dodecamethyl-cyclohexasiloxane	91	-
14	13.991	899	Tetradecamethyl-hexasiloxane	81	-
15	15.172	1011	Dodecamethyl-pentasiloxane	33	Silicone oligomers fragment
16	16.146	1106	Hexadecamethyl-heptasiloxane	50	-
17	17.286	1218	Tetracosamethyl-cyclododecasiloxane	52	-
18	18.063	1292	Tetracosamethyl-cyclododecasiloxane	27	Silicone oligomers fragment
19	19.110	1393	Octadecamethyl-cyclononasiloxane	74	-
20	19.794	1459	Hexadecamethyl-heptasiloxane	86	-
21	20.063	1485	Un-identified	-	m/z 327, 405, 156, 343, 253
22	20.737	1550	1,1,1,5,7,7,7-heptamethyl-3,3-bis(trimethylsiloxy)tetrasiloxane	43	-
23	21.369	1611	Hexadecamethyl-heptasiloxane	59	Silicone oligomers fragment
24	21.452	1619	Un-identified Note 1	-	m/z 135, 197, 479, 329, 73

Peak number	RT (min)	Scan number	Peak ID (Wiley07/Nist5)	% Fit	Comment
25	22.208	1692	Tetracosamethyl-cyclododecasiloxane	50	Silicone oligomers fragment
26	22.820	1750	Hexadecamethyl-heptasiloxane	59	Silicone oligomers fragment
27	23.006	1768	Un-identified Note 1	-	m/z 135, 197, 73, 403, 341
28	23.545	1820	Un-identified	-	m/z 73, 355, 221, 147, 429
29	24.146	1879	Hexadecamethyl-heptasiloxane	10	Silicone oligomers fragment
30	24.509	1914	Un-identified Note 1	-	m/z 135, 73, 197, 209, 327
31	24.778	1939	Octadecamethyl-cyclononasiloxane	53	Silicone oligomers fragment
32	25.380	1998	Tetracosamethyl-cyclododecasiloxane	22	Silicone oligomers fragment
33	25.939	2051	Tetracosamethyl-cyclododecasiloxane	64	Silicone oligomers fragment
34	26.530	2109	Hexadecamethyl-heptasiloxane	33	Silicone oligomers fragment
35	27.027	2156	Octadecamethyl-cyclononasiloxane	59	Silicone oligomers fragment
36	27.131	2167	Un-identified Note 1	-	m/z 135, 73, 147, 221, 283
37	27.639	2215	Un-identified	-	m/z 221, 147, 73, 295, 369
38	28.126	2262	Octadecamethyl-cyclononasiloxane	72	Silicone oligomers fragment
39	28.437	2292	Un-identified	-	m/z 451, 218, 389, 373, 156
40	28.851	2333	Hexadecamethyl-heptasiloxane	25	Silicone oligomers fragment
41	29.245	2371	Un-identified	-	m/z 197, 135, 259, 451
42	29.349	2381	Tetradecamethyl-hexasiloxane	47	Silicone oligomers fragment
43	29.794	2424	Un-identified Note 1	-	m/z 135, 73, 147, 221, 281
44	30.271	2469	Un-identified	-	m/z 221, 147, 73, 295, 369
45	30.385	2481	Un-identified	-	m/z 197, 135, 259
46	30.592	2501	Un-identified	-	m/z 197, 135, 465, 73, 259
47	30.768	2517	Octadecamethyl-cyclononasiloxane	91	Silicone oligomers fragment
48	31.400	2579	Un-identified Note 1	-	m/z 135, 73, 147, 221, 207
49	32.022	2639	Hexadecamethyl-heptasiloxane	40	Silicone oligomers fragment
50	32.354	2670	Un-identified Note 1	-	m/z 135, 197, 73, 207, 465
51	32.489	2684	Octadecamethyl-cyclononasiloxane	87	Silicone oligomers fragment
52	33.328	2765	Un-identified Note 1	-	m/z 135, 73, 147, 221, 207

Peak number	RT (min)	Scan number	Peak ID (Wiley07/Nist5)	% Fit	Comment
53	34.271	2856	Hexadecamethyl-heptasiloxane	50	Silicone oligomers fragment
54	34.623	2890	Octadecamethyl-cyclononasiloxane	72	Silicone oligomers fragment
55	37.318	3149	Octadecamethyl-cyclononasiloxane	90	Silicone oligomers fragment
56	40.758	3480	Un-identified	-	m/z 221, 147, 73, 281, 355
57	41.069	3511	Hexadecamethyl-heptasiloxane	38	Silicone oligomers fragment
58	45.163	3907	Octadecamethyl-cyclononasiloxane	72	Silicone oligomers fragment
59	46.230	4013	Hexadecamethyl-heptasiloxane	38	Silicone oligomers fragment

Note 1 un-identified compounds but related fragments

Peaks in **bold** text appear in the solvent blank

Table 6 Direct Headspace Analysis

Peak number	RT (min)	Scan number	Peak ID (Wiley07/Nist5)	% Fit	Comment
1	11.5	1096	Acetone	9	-
2	13.0	1239	Methoxytrimethylsilane	64	-
3	14.6	1392	Dimethylsilanol	78	-
4	16.0	1526	Carbon Disulfide	9	-
5	18.0	1715	Trimethylsilanol	78	-
6	18.2	1736	Methoxytrimethylsilane	78	-
7	20.2	1922	1,1,3,3-tetramethyldisiloxane	81	-
8	23.6	2251	1,1,1,3,3-pentamethyldisiloxane	80	-
9	25.5	2435	Cyclohexane	94	-
10	29.3	2794	2-methoxybenzoic acid methyl ester	43	-
11	31.3	2988	Toluene	76	-
12	31.6	3019	Unidentified	-	m/z 149, 133, 75
13	32.5	3100	1,1,3,3,5,5-hexamethyltrisiloxane	70	-
14	33.8	3224	Hexamethylcyclotrisiloxane	87	-
15	36.8	3511	Ethylbenzene	60	-
16	37.3	3560	1,3-dimethylbenzene (o/m/p-xylene)	95	-
17	38.9	3717	o/m/p-xylene	81	-
18	44.0	4197	1,1,3,3,5,5-hexamethyltrisiloxane	53	-
19	44.9	4286	octamethylcyclotetrasiloxane	91	-
20	46.3	4423	2,2,4,6,6-pentamethylheptane	50	-
21	51.1	4878	2,2,4,4,6,6,8,8,10,10-decamethylcyclopentasiloxane	46	-
22	55.4	5289	Dodecamethylcyclohexasiloxane	91	-
23	59.5	5679	1,1,3,3,5,5,7,7,9,9,11,11-dodecamethylhexasiloxane	40	-
24	64.4	6147	1,1,3,3,5,5,7,7,9,9,11,11,13,13-tetradecamethylheptasiloxane	25	-

Table 7 Quantification of volatile organics

	Peak RT	Peak Response	Peak Concentration (µg/g ppm)	Wiley07/NIST05 Identification
	Prep 1 (AA07)			
1	11.526	1787527	0.107	Acetone
2	16.064	953441	0.057	Carbon Bisulfide
3	25.548	11905608	0.711	Cyclohexane
4	29.240	1029064	0.061	2-methoxybenzoic acid methyl ester
5	31.320	1752667	0.105	Toluene
6	31.645	2017057	0.120	Unidentified
7	36.800	2168678	0.130	Ethylbenzene
8	37.281	8883004	0.530	1,3-dimethylbenzene (o/m/p-xylene)
9	38.944	3643856	0.218	o/m/p-xylene
10	46.326	3150583	0.188	2,2,4,6,6-pentamethylheptane
	Prep 2 (AA08)			
1	11.505	2159824	0.135	Acetone
2	25.548	15579873	0.972	Cyclohexane
3	29.281	1260895	0.079	2-methoxybenzoic acid methyl ester
4	31.331	1542741	0.096	Toluene
5	31.634	2047111	0.128	Unidentified
6	36.800	2484450	0.155	Ethylbenzene
7	37.281	9394702	0.586	1,3-dimethylbenzene (o/m/p-xylene)
8	38.944	4253436	0.265	o/m/p-xylene
9	46.326	2064747	0.129	2,2,4,6,6-pentamethylheptane

	Peak RT	Peak Response	Peak Concentration (µg/g ppm)	Wiley07/NIST05 Identification
	Prep 3 (AA09)			
1	11.546	1388574	0.088	Acetone
2	25.538	15439040	0.978	Cyclohexane
3	29.292	1209338	0.077	2-methoxybenzoic acid methyl ester
4	31.331	979073	0.062	Toluene
5	31.645	2185112	0.138	Unidentified
6	36.789	2068264	0.131	Ethylbenzene
7	37.270	9737593	0.617	1,3-dimethylbenzene (o/m/p-xylene)
8	38.954	3698333	0.234	o/m/p-xylene
9	46.358	1528951	0.097	2,2,4,6,6-pentamethylheptane

APPENDIX 1

Analytical methodology for solvent extraction method

Column (Analytical)	30 m x 0.25 mm x 0.25 µm J & W DB5-MS column
Flow rate	Helium @ 10 psi (constant)
Liner	Agilent Cat no. 5181-3316
Split/splitless	Splitless mode
Injector temperature	300°C
Injection volume	1µL
Purge vent	On @ 50 mL/min @ 0.6 min
Oven programme	50°C for 2 min, then 10°C/min to 300°C hold for 20 min
Transfer line	300°C
MSD settings	
Mass scan range	35 to 500 AMU
Scan rate	1.6 scans/second
Data collection	4.6 to 47 min

Analytical methodology for head-space for GC-MSD

Head-space parameters

Equilibration temperature	85°C
Equilibration time	60 min
Transfer line temperature	110°C
Sample pressure	Adjust vial pressure to >5psi above column head pressure
Pressure time	90 sec
Shaker	On
Needle temperature	110°C
GC cycle time	75 min
Injection time	12 sec
Withdrawal time	30 sec
Vial venting	On

GC parameters

Column (Analytical)	Agilent J&W, DB-1, 60m x 0.32mm, film thickness 5µm with 2 m retention gap
Liner	Silitek 1mm
Carrier gas	Helium @ 13psi constant
Injection type	Split
Split ratio	1:1
Injector temperature	250°C
Oven temperature	35°C for 10 minutes Then 5°C/min to 150°C hold for 10 minutes Then 15°C/min to 250°C hold for 1 minute Then 30°C/min to 280°C hold for 18.33 minutes
Transfer line temperature	250°C

MSD settings

Mass scan range	35 to 500 AMU
Scan rate	1.6 scans/second
Data collection	4.6 to 37 min

To the UK's Department of Health
and to whom it may concern,
on behalf of the PIP Action Campaign.

Subject: information requested in relation to concerns surrounding fraudulent PIP and rebranded-PIP silicone breast implants.

The information and opinions I have collected in relation to the PIP situation since April 2010, together with the unpublished results of investigations (past and ongoing), justify my expressing the following main areas of concern in relation to UK/EU policy specifically:

1. The advice that for implanted women it is safe to breastfeed is illogical: while understanding the need to strike a risk/benefit balance, I believe the advice still constitutes, at best, an unacceptable failure to observe the precautionary principle; and at worst, it is positively dangerous. The main problem for me, aside from whether the various chemical compositions of the filler may or may not be dangerous, is that ultrasound is (and has long been) known to significantly fail to provide any degree of certainty that the implant is not ruptured or leaking. Both Professor Keogh's and SCENIHR's reports fail unacceptably in this regard: the safety advice is simply illogical.

2. There can be no justification for not warning the populations of the UK and other countries of the presence on the market of rebranded (and therefore not identifiable among implantees) PIP implants. My concerns relate especially to the failure to recognise the need to warn UK women about rebranded PIP implants, notably Rofil, but also internationally of the titanium-coated "TiBreeze" PIPs, and potentially other PIP rebrands that I firmly suspect have been marketed around the world from countries outside the EU. In the UK, it is fair to assume that Rofils alone may have been used in around 5,000 women, given the size and spread of the international cosmetic surgery market. So, barring probably very small exceptions, if any at all, they will have been implanted abroad, but they needed to be alerted in order to seek appropriate follow-up. There is, I understand, an obligation across the EU as a single market to alert all consumers; whether or not this is the case, the nature of the cosmetic industry and the scale of the PIP/Rofil problem justified alerting UK women. In late 2011, I reported that certain EU states were likely still implanting Rofil-rebranded PIPs, which proved to be correct.

3. The unrecognised international scale of the problem, which the UK, as an admired government/democracy globally, should have been more proactive in helping to divulge for global benefit.

And on issues of general criticism, I wish to state that:
4. Private healthcare providers should be severely punished wherever they have failed to alert and follow up their patients. The government has singularly failed many thousands of women in this regard.

5. In relation also to this last point, insufficient weight has been placed at a policy-making level to recognise and act on the clearly huge clinical- and cost-effectiveness benefits of detecting ruptures/leaks sooner and to explant, with the precautionary principle in mind.

6. The delays in acting in all of the above areas since April 2010 cannot be justified if the precautionary principle is applied correctly, and must therefore be criticised in the strongest terms, and be learned from accordingly. Current official policy does not overtly reflect this.

Attachments in support of this statement of concerns (cbm = Clinica, Bernard Murphy):
cbm6317 - 13.5.10 - 600,000 implants per year – PIP's 2008 output target
cbm7226 - 15.2.11 - Rebranded PIP breast implants 'many women in UK and other countries unaware of risks'
cbm - 21.2.11 - MHRA “prepared to review PIP breast implant guidance” to reflect Rofil rebranding
email to DH, 4.1.12 – “PIP breast implants situation - FAO Professor Sir Bruce Keogh”
email to SCENIHR, 18.1.12
cbm - 31.1.12 - Ultrasound failing PIP scans, MRI the key – but question mark hangs over capacity
cbm8417 - 19.3.12 - Rofil PIPs implanted in 61 women post-Dutch warning, Estonia survey reveals

The above opinions and the information that is provided in support of them are shared publicly on the basis that they are deemed by myself to be of significant public (and public health) interest.

The views expressed here stem from my work (published and otherwise) for Clinica Medtech Intelligence, but that they are nevertheless submitted as personal, as is everything related to my contribution to the PIP debate outside of what I formally publish via Clinica.

Bernard Murphy
international markets & investigations editor,
Clinica Medtech Intelligence

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From: Murphy, Bernard
Sent: 18 January 2012 16:10
To: Sanco-SCENIHR-Secretariat@ec.europa.eu
Subject: Rapid scientific opinion on the safety of PIP breast implants

Subject: Rapid scientific opinion on the safety of PIP breast implants

Dear SCENIHR,

I have read with interest the *Request for a rapid scientific opinion on the safety of PIP breast implants*, and feel that it is incumbent upon me, from a public health interest perspective, to share with you any relevant information I may have collated during my constant monitoring and investigation of the PIP/Rofil situation since March 2010.

I have a vast amount of raw information, correspondence, patient views (having joined and interact with several patient support groups around the world), PIP documents and so on; we have published on the basis of some of it, but much is raw information that provides important background context to the wider situation, globally - such as regarding the outsourcing/ rebranding activities involving PIPs.

Without wishing to overwhelm the committee with the buk of that information, here follows a summary of the concerns that stem from two main areas of concern. The gaps in data that underlie these have clearly resulted in omissions in precautionary public health policy.

1. Rebranding of PIP implants.
One is the fact, scale and implications of the rebranding of PIP implants (notably as M-implants, by Rofil Medical Nederland, as warned in April 2010 by the IGZ), and the extent to which it has been underestimated internationally. I am currently investigating a number of potential rebranding links to PIP.

We have been approached by patients in a number of countries regarding the rebranding issue specifically, and our information has been requested by, among other people, experts close to the French health ministry's recent PIP policy review.

As far as I am aware, the statement issued on 23 December 2011 by IPRAS (which we have approached in the past regarding PIP and Rofil) is the first international statement of global reach to highlight the PIP/Rofil link. Coincidentally, a number of countries have begun to survey more closely the PIP 'market' for the current/past presence of Rofil's M-implants.

The impact of failing to acknowledge and warn about the Rofil rebranding means, quite obviously, that Rofil patients may remain completely unaware that they have PIP implants, and are therefore not likely to monitor their implants preventively or to address symptons with the diligence that other PIP implantees are being advised to adopt. This problem is exacerbated by any prevarication on the part of clinics and plastic surgeons in addressing patient concerns.

The number of EU implantees of Rofil-rebranded PIPs is potentially significant, especially among clinics that operate in Europe's large cosmetic surgery tourism market.

UK, spanish and French breast implantees have cited *Clinica* reporting as their first and only insight into Rofil Medical's rebranding of PIPs and, consequently, the trigger of precautionary follow-up enquiries. For at least for one UK patient, our reporting was the basis of her decision to scan the breast and explant after severe damage to the breast.

2. The global scale of the PIP problem.
Although the precise data on the scale of PIP implant use remains hazy, I have reason to believe that the figures being cited officially are significantly under-estimating the problem, and that the number of women affected globally is easily several hundred thousand. I feel that this is important because the scale of the global problem has an impact on the overall, 'interrelated' evolution of policy.

Some "official" estimates put the global figure at around 300,000; one cosmetic industry expert who was recently advising the UK government said that the global number is 100,000. It may have been a slip of the tongue, but I do feel that it is important 'internationally' that the figure (or estimate range) is realistic, if not perfectly correct, and that any errors are over-estimates rather than under-estimates, so that (precautionary priniciple) policies may best address the seriousness of what is a global situation.

I believe the global figure is more likely to be in the order of 600-700,000, at least. Personally, if it reaches 1 million, it will not surprise me. I have reported these estimates from calculations of the ratios of export versus domestic market production, as declared by Heritage in 2007, compared with official PIP/market data for France alone.

My primary sources include documentation I saved from the PIP website, just before the French authorities closed the company in late March 2010, and from Heritage Worldwide, the US-based parent company of PIP, in the form of formal trade data (10-K and other SEC filings) and investor statements.

The figures that I'm working with (collated since April 2010) are: 65 or 66 countries, 46 distributors and at least one subsidiary (Spain's PIP España, which closed in 2009). In 2007, PIP claimed to be exporting more than 160,000 implants per year, and that by the end of 2008, it was planning to increase production to 600,000 per year (exporting 84%), as reported by *Clinica*.

Some examples of the provisional number of implantees in just a handful of countries:
UK: 40-45,000 (surely more, based on 80,000 implants halved, plus a proportion of unilateral implantations - and not including Rofil implantees);
France: 30,000
Venezuela: ovre 62,000, according to the national cosmetic surgery society; officially, 33,000.
Brazil: 25,000 (plus, now, figures for implantees of Rofil-rebranded PIPs?)
Colombia: 15,000 (just from 2008, according to government figures)
Argentina: 13,000
Spain: 12,000? (in the Valencia region alone there are 9,600)
Australia: 5,000.

Given the tentative nature of the current estimates (and the lack of coherence in the data), I will not be surprised if the national figures are far higher, especially in certain countries that were deemed to be commercially more important for PIP than the UK or France, for example. Latin America was said to account for around 50% of PIP exports. The revision of the picture in the last week alone in Brazil, Venezuela and Colombia (as indicated in the list), appears to justify the perception that national patient numbers are set to rise in the region.

Finally, I feel certain that most of the 65-66 countries where PIPs were sold are (or will be) looking to the EU and its worst-affected member states to adopt the strongest precautionary thinking approach to the PIP crisis.

I remain at your disposal for any further help or information I may be able to provide.

Yours,
Bernard

Bernard Murphy
international markets & investigations editor,
Clinica Medtech Intelligence

From: Murphy, Bernard
Sent: 04 January 2012 19:09
To: julia.harris@dh.gsi.gov.uk
Subject: PIP breast implants situation - FAO Professor Sir Bruce Keogh

Follow Up Flag: Follow up
Flag Status: Flagged

FAO Professor Sir Bruce Keogh, NHS Medical Director,
(as adviser to the government on the PIP breast implants situation)

Dear Professor Keogh,
in view of the advice being courted by the government on the PIP breast implants situation, I write in the hope of helping to fill the complex and far-from-complete international picture, based on my experience of the situation since early 2010, in my capacity as markets/ investigations editor for *Clinica Medtech Intelligence*.

Among the gaps in data, and what I see as a resulting omission in precautionary public health policy, I would like to point out what I see as two very important elements:

1. Rebranding of PIP implants.
One is the fact, scale and implications of the rebranding of PIP implants (as M-implants at least, by Rofil Medical in the Netherlands), and the extent to which it has been underestimated internationally.

Clinica has long sought to alert (and respectfully challenge) the MHRA on this issue. In the light of the evidence at my disposal, the dismissal of this component of the PIP crisis by the MHRA, among other agencies, is both mystifying and disturbing. Given the important role-model that the MHRA arguably embodies internationally, its position must surely be impacting negatively on international policy.

We have been approached by patients in a number of countries regarding the rebranding issue specifically, and our information is now also being requested to inform, among other things, this week's French health ministry PIP monitoring committee meeting.

As far as I am aware, the statement issued on 23 December 2011 by IPRAS (which we have approached in the past regarding PIP/Rofil) is the first international statement of global reach to highlight the PIP/Rofil link. Coincidentally, a number of countries have begun to survey more closely the PIP 'market' for the current/past presence of Rofil's M-implants.

The impact of failing to acknowledge and warn about the Rofil rebranding means, quite obviously, that Rofil patients may remain completely unaware that they have PIP implants, and are therefore not likely to monitor their implants preventively or to address symptons with the diligence that other PIP implantees are being advised to adopt. This problem is exacerbated by any prevarication on the part of clinics and plastic surgeons in addressing patient concerns, as has been criticised by the government itself.

The number of UK implantees of Rofil-rebranded PIPs is potentially significant among the 5,000 women who travel abroad every year for the cheaper cosmetic surgery that is associated with PIP/Rofil implants, and during the nine-year period affected by the recall/ban.

UK breast implantees have cited *Clinica* reporting as the basis of their 'medical' decision-making, as well as the source of knowledge on PIP and, consequently, the trigger of precautionary follow-up enquiries. While I am honoured to make any contribution to public health through my work, this is surely not an acceptable state of affairs.

2. The global scale of the PIP problem.

Although the precise data on the scale of PIP implant use remains hazy, I have reason to believe that the figures being cited officially significantly underestimate the problem, and that the number of women affected globally is easily several hundred thousand.

Some "official" estimates put the global figure at around 300,000; one cosmetic industry expert who is currently advising the government said (during a BBC TV interview yesterday) that the global number is 100,000. It may have been a slip of the tongue, but I do feel that it is important 'internationally' that the figure (or estimate range) is realistic, if not perfectly correct, so that policies reflect the seriousness of the situation.

In just a handful of countries, the official government estimates easily exceed 100,000:
UK: 40,000 (surely more, based on 80,000 implants halved, plus a proportion of unilateral implantations - and not including Rofil implantees);
France: 30,000
Brazil: 25,000
Argentina: 13,000
Spain: 8-12,000.

Given the tentative nature of the current estimates (and the lack of coherence in the data), I will not be surprised if the national figures are far higher, especially in certain countries that were deemed to be commercially more important for PIP than the UK or France, for example. Latin America was said to account for around 50% of PIP exports.

I should also point out that in 2007, PIP claimed to be exporting more than 160,000 implants per year, and that by the end of 2008, it was planning to increase production to 600,000 per year (exporting 84%), as reported by *Clinica* (source: SEC filing by PIP's parent company, Delaware-based Heritage Worldwide).

The number of countries where PIPs were sold is around 65. I suggest that most of these countries will be looking to the likes of the UK and France to apply the tightest degree of precautionary thinking, as the PIP situation appears to demand.

I remain at your disposal for any further help I may be able to provide.

Yours,

Bernard Murphy
international markets & investigations editor,
Clinica Medtech Intelligence

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Ultrasound failing PIP scans, MRI the key – but question mark hangs over capacity

Bernard Murphy, Clinica Medtech Intelligence

31 January 2012

There is growing evidence that ultrasound is failing to show ruptures, leaks and seepage of silicone in PIP breast implantees clearly enough to provide a basis for the extremely important medical decisions that the monitoring is intended to provide.

While explantation is delayed in favour of the watch-and-wait approach that all but a handful of countries are advocating, then magnetic resonance imaging (MRI) should instead be the imaging technology of choice. However, any shift in policy – as is already beginning to emerge – would depend on any given health system having the necessary capacity. The UK, for example, could not handle, six-monthly MRI scanning of upward of 40,000 women, an industry expert has told *Clinica*.

“MRI is the method of choice for investigating problems associated with silicone breast implants, most specifically leaks of the silicone from the implant capsule into surrounding tissue,” Professor Andrew Jones, vice-president of the British Institute of Radiology (BIR) and chair of the BIR’s MR Safety Working Party, told *Clinica*.

“MRI is superior to ultrasound imaging for the assessment of suspected leaks from silicone implants and for the interpretation of abnormal folding of the implant,” he added.

“MRI allows sensitive interpretation of any abnormalities in the structure of the implant capsule, in addition to showing areas where silicone may have leaked from the implant capsule into surrounding tissues”, he explained. “The underlying principles that support these techniques will not be affected by the possible presence of chemical impurities within the silicone.”

“MR imaging of silicone implants relies on the fact that the MR systems can detect differences in signals arising from water, fat and silicone. As such it is possible, utilising specialised scanning techniques, to produce a variety of images of the breast that can either suppress signals from silicone or suppress signals from water and fat, leaving only silicone signal within the images,” said Professor Jones.

Ruptures and non-rupture leaks are a relatively common effect of the more liquid fraudulent industrial-grade silicone filler that is thought to have been used by French maker PIP over much of the last decade. The failure to recognise and record these device failures through is providing false reassurance to many women around the world and, crucially, to infants, given the known risk from breastfeeding with failed PIPs.

MRI is believed by experts to be the key, because it can be done to "see" only the silicone, and hence whether it is outside the implant capsule, or even migrated to the lymph nodes. PIP silicone is far more fluid than normal medical-grade implant silicone, so leaks/seepage especially will be less likely to show in normal interpretations of the scans. In any case, ruptures are being missed, a fact that is being increasingly noted by patients around the world and by the scientific community.

Policy shifts towards MRIA shift in PIP implant monitoring policy towards a clearer reliance on MRI has already emerged: A revised case-handling protocol and a technical guideline unveiled by Brazil this week calls for certain inconclusive ultrasounds to be followed up by an MRI scan (www.clinica.co.uk, 26 January 2012).

In the only other example that *Clinica* is aware of, the Dutch healthcare inspectorate (IGZ) and the country’s plastic surgery society (NVPC) have similarly advised in a joint statement that MRI and not ultrasound is the recommended method for assessing PIP implantees.

Official explantation data already appears to confirm these fears: France's Afssaps agency recently reported that among 672 implant removals requested by the patient – ie not recommended from the implant's monitoring – 23 cases of rupture and 14 of leakage without rupture were identified.

Rofil PIPs implanted in 61 women post-Dutch warning, Estonia survey reveals

At least 61 women received Rofil-rebranded PIP breast implants in Estonia as recently as 2011, the country's healthcare products regulatory agency, Terviseamet, has announced. The figure is among the results of a survey it has conducted on the use of PIP and Rofil 'M-implant' devices among the country's 13 cosmetic surgery providers.

The findings, part of an ongoing investigation, confirm concerns raised by Finnish authorities that the banned PIPs were still being implanted in late 2011. This was in spite of alerts having been circulated across the EU as far back as April 2010 concerning both the fraudulent silicone filler of PIP implants and their possible circulation under a different name. The situation – details of which remain unclear – suggests shortcomings in the EU's device alerting system and/or an inability on the part of member states to oversee trade across the common market.

The survey found that 364 women received a total of 732 French-made Poly Implant Prothèses (PIP) implants or their Rofil-rebranded equivalents. Of these, 163 patients received PIPs at two clinics. Terviseamet believes that PIP-branded implants have not been used since the end of March 2010, following the recall and ban by French regulatory agency Afssaps.

The remaining 200 women recorded by the survey received M-implants: 139 women were implanted during 2004-09 – ie prior to either the PIP alert or the M-implant alert issued by Dutch regulatory agency IGZ on 19 April 2010. However, one clinic has reported implanting 61 women with Rofil M-implants during 2011.

Terviseamet has said that it could not contact one of the providers, meaning that the figures may not be definitive. It is not clear either whether these data take account of "cosmetic tourism" cases: Eastern Europe is known to have been a common destination for women from other parts of Europe and beyond.

Prior to the survey, it was previously thought that around 150 women had received PIPs (under the original PIP brand) in Estonian clinics. Terviseamet launched its investigation when a Finnish patient was reportedly found to have Rofil-branded implants she received in around October 2011, with a device code number that was listed as banned by Afssaps.

In a further twist, the survey has also confirmed suspicions that the M-implants were not imported from Breda, Netherlands-based Rofil Medical Nederland (the subject of the IGZ's April 2010 recall and ban). Instead, the Estonian devices were imported from a Cyprus-based successor, established as Rofil Medical Implants, according to Terviseamet.

Previous uncorroborated reports suggested that these Cypriot M-implants were imported from a South Korean supplier (www.clinica.co.uk, 11 January 2012). This was not confirmed by Terviseamet in its 27 February announcement of the results of the survey. However, its investigations are ongoing, the agency said.

The first sign of international concern at the possible circulation of Rofil implants outside the Netherlands was raised by Portuguese regulatory agency Infarmed in August 2010 (www.clinica.co.uk, 18 August 2010). Last month, Brazil's Anvisa announced that three distributors had supplied Rofil silicone implants for around a decade, prompting a radical review of follow-up policy and a wave of discussion among at least a dozen regulatory agencies (www.clinica.co.uk, 12 January 2012).

Rebranded PIP breast implants – many women in UK and other countries "unaware" of risks

Bernard Murphy
Clinica Medtech Intelligence, 15.2.11

Many women in the UK – and other countries – remain unaware that they carry illegal silicone breast implants made by French maker Poly Implant Prothèse (PIP), marketed under a different brand, *Clinica* has learned.

Evidence has emerged that PIP implants rebranded by Dutch firm Rofil Medical have been widely used by "health tourism" clinics around the world. This means that the number of women affected by the PIP fraud internationally – officially 50,000 in the UK alone and 30,000 in France, for example – is likely to be significantly greater than previously thought.

Since PIP warnings do not mention the Rofil rebranding, these women remain largely unaccounted for and unprotected in terms of follow-up care. The health risks for these PIP implantees could become even more serious if the filler proves to be genotoxic in ongoing tests by French regulatory agency Afssaps.

Clinica was alerted to the unaddressed risk to Rofil implantees when a UK patient contacted to ask whether M-implants should be considered as hazardous as PIP. She cited *Clinica*'s article (www.clinica.co.uk, 18 August 2010) on Portugal's response to an alert issued by Dutch regulator IGZ in April 2010. In its alert, IGZ reported that Breda-based Rofil Medical Nederland had bought PIP's fraudulent implants and resold them internationally under the name "M-implant".

The patient was implanted in Brussels in 2006 and found out in July 2008 that both implants had ruptured, probably some time earlier. The implants were found to be surrounded by scar tissue and, in the belief that they posed no major risk, she opted to not explant them, though silicone had already been found in a number of lymph nodes, which were then removed. She changed her mind in response to *Clinica*'s coverage, and is about to undergo urgent replacement surgery.

She is one of an estimated 5,000 UK women who travel abroad for breast augmentation annually.

The British Association of Aesthetic and Plastic Surgeons (BAAPS) believes that the Rofil rebranding poses a significant new concern, noting that PIP implants were "known to have been popular with the larger domestic chains and commercial clinics because of their low cost". Yet, the extent of the presence of these rebranded implants appears to have been ignored by most regulatory agencies, on the basis that they were not distributed in their respective countries.

"The discovery that the rupture-prone products were also sold in countries such as Belgium and [other leading cosmetic surgery destinations] under the rebranded name Rofil M-implant could mean that the number of women who should be on the alert is much higher," a spokesperson said.

"PIP advice to be extended" – BAAPS

In light of *Clinica*'s findings, BAAPS said it will now issue a warning to women who have travelled abroad for breast augmentation. Citing the current advice on PIP, the association's president, Fazel Fatah, said the association would "reiterate its advice and extend it to women who may have gone abroad for their surgery".

The international guidelines for women with PIP implants – whether or not these have ruptured – is to undergo immediate examination to assess the condition of the implant shell, followed by regular checks, including MRI scans. Ruptured implants should be removed immediately; women with one ruptured implant are advised to have both removed.

This is provisional advice, subject to ongoing genotoxicity tests on the filler. French regulator Afssaps has said it expects to publish the results in "early 2011" and, if they show an increased risk of harm, then the advice will likely be to recommend immediate explantation in all cases.

The UK Medicines and Healthcare products Regulatory Agency (MHRA) did not reissue the IGZ's warning for the UK – and thereby extend its PIP guidance to Rofil implantees – on the basis that the rebranded devices were deemed not to have been supplied in the UK. The agency stands by this position.

“The MHRA has no evidence to suggest that any Rofil-branded silicone breast implants were implanted in the UK,” the agency told *Clinica*. “The MHRA’s remit is to ensure the safety of devices implanted in the UK. We do not therefore consider it necessary to alter our advice.”

Rofil escalation – a new global regulatory challenge

The Rofil rebranding problem affects many countries within the EU and around the world, but only Portugal appears to have publicly alerted its healthcare system to the problem (www.clinica.co.uk, 18 August 2010). This was apparently due to Rofil appearing in patients who had undergone operations abroad. Portuguese regulator Infarmed said that Rofil-rebranded PIP implants had not been supplied in the country.

In France and Spain, PIP patient support groups and experts representing them in these countries, have told *Clinica* that they are unaware of the existence of Rofil-branded PIPs or of the history surrounding them.

However, health tourism websites have been advertising Rofil silicone gel implants or listing their suppliers throughout the last decade, in particular between 2003 and 2009. This is true of some of the most popular destinations such as the Czech Republic, Poland and the Far East, but also even in the US, *Clinica* can reveal (further details to follow, subject to discussions with the FDA).

Clinica cannot confirm whether the implants marketed by these sites were fraudulent or unsafe, but they were being marketed within the timeframe of the PIP ban and appear to fall under IGZ’s Rofil M-implant alert of April 2010, in terms of the type of implants involved, namely “cohesive silicone gel” and their marketing descriptions.

So far, the focus of this crisis has been the implants sold by PIP directly in at least 65 countries over nine years (www.clinica.co.uk, 13 May 2010). However, the growing evidence that Rofil-branded PIP silicone implants have been supplied to the health tourism industry around the world is a major source of concern, by leaving many women unaccounted for in health protection advice and follow-up care.

The situation suggests the need for a radical rethink of national and international surveillance and alerting policies, as well as an immediate review of PIP-related guidance to reflect the rebranding problem.

@f
600,000 implants per year – PIP output target in 2008
..
Poly Implant Prothèse (PIP), the now defunct manufacturer of fraudulent silicone breast implants, was producing some 160,000 implants per year in early 2007, and was set to increase production to 600,000 units by the end of 2008, *Clinica* has learned.

The figure is important in seeking to gauge the global scale of the crisis affecting these devices. In addition to concerns about the filler itself, which is currently under investigation, there is virtually no information in the public domain about the number of women affected in each of the vast majority of the countries where the implant was distributed, and their traceability. Data available on the PIP website immediately before it was shut down, on or around 1 April, suggested that the devices were being sold in 66 countries.

PIP's efforts to expand production capacity are described in statements issued by its parent company, Heritage Worldwide, to investors in March 2007. Signed by CEO Jean-Claude Mas, they note that Heritage/PIP had "made substantial headway into Brazil and Argentina" and that "[while] we continue to do well in Europe, we have made significant inroads into Australia and Asia".

The statement, dated 27 March 2007, goes on to say that the focus of Heritage/PIP at the time was to expand into Asia and Latin America. These markets were described as "growing very rapidly". It states that the expansion programme would result in a 275% increase in production. At the time, it had national distributors in 63 countries, in addition to a Spain-based subsidiary.

All PIP silicone implants produced as far back as 2001 are affected by the concerns raised on 30 March 2010 by French regulatory agency Afssaps, in view of the fact that the La Seyne-sur-Mer firm is not able to demonstrate at what point it began to use an illegal silicone filler after the device's CE marking.

"Implant collapse" in Australian case
Australian patient Marlene Fabris, who underwent a second PIP implant replacement on 11 May in Melbourne, has told *Clinica* that the failure was found to have been due to the implant collapsing on itself, and not a rupture.

This second PIP failure occurred only five weeks after the first, which occurred 14 weeks after implantation (www.clinica.co.uk, 11 May 2010), and the implant is understood to be under investigation.

The national regulatory body, the Therapeutic Goods Administration (TGA), gave PIP approval to market its silicone breast implants in Australia in November 2004. The implants were distributed solely, *Clinica* understands, by Medical Vision Australia, based in Hackney, South Australia.

"Australia, with more than 20 million people and a higher GDP than France, provides a healthy platform for our products, and a springboard to enter into other Asia-Pacific countries," said PIP's CEO Mr Mas at the time.

[Final version, updated 21.2.11]

MHRA “prepared to review PIP breast implant guidance” to reflect Rofil rebranding

Breast implants marketed by Dutch firm Rofil, currently under the spotlight in Europe for their association with the fraudulent silicone implants made by Poly Implant Prothèse (PIP) of France, have been implanted in the UK, *Clinica* has learned.

Legal evidence revealed to *Clinica* suggests that the UK's Medicines and Healthcare products Regulatory Agency (MHRA) will be forced to issue a warning about the existence of Rofil-branded implants on the market, and about the risk that they might contain the illegal PIP filler. Healthcare professionals in the private sector as well as the NHS would be warned, as would breast implantees in the UK – and possibly internationally. The legal evidence is said to have been presented to the MHRA.

Rofil-PIP hydrogel implants were certainly used in patients in Northern Ireland, according to a UK lawyer with long-standing experience of breast implant defect cases. Paul Balen, of the Nottingham law firm Freeth Cartwright, told *Clinica* that they were implanted by a Dutch surgeon.

It is not known whether Rofil implants specifically containing PIP's fraudulent silicone have ever been implanted in the UK, but the MHRA says it will consider reviewing its PIP guidance, if any Rofil-branded implant – whether hydrogel or silicone – can be shown to have been used in the UK.

"The MHRA has no evidence that any Rofil-branded breast implants were implanted in the UK," the agency said in response to the evidence, as cited by Mr Balen, that "Rofil-PIP" hydrogel breast implants had been implanted in at least one UK patient.

The agency added: "If evidence comes to MHRA's attention that Rofil breast implants have been implanted in the UK the MHRA will consider the need to issue further advice."

In response to evidence that many UK women are likely to have received Rofil implants abroad, the MHRA had said it did not consider it necessary to change its guidance (www.clinica.co.uk, 15 February 2011).

Mr Balen is an expert in PIP breast implant defects, having acted as a lawyer in class actions dating back to the early 2000s involving Trilucent soya-oil breast implants, then PIP and Rofil-PIP hydrogel implants and now PIP silicone implants.

"If I had known that the MHRA was not going to warn about Rofil on the basis that Rofil implants are not used in this country, I would have told the MHRA they were wrong, because I know that [the implants] are," said Mr Balen.

"I may only know that one pair are, but the mere fact that I know one case, as just one solicitor with a handful of cases, suggests there may be more," he said. "It cannot protect consumers in this country to presume that [Rofil is not available]," he added.

The information revealed by Mr Balen, which stems from legal evidence in at least one case, suggests there may well have been a direct supply link between the Dutch surgeon and the Breda-based Dutch firm Rofil without involving a UK distributor as intermediary. There appears to be no record of a UK-based Rofil supplier.

This situation would explain the agency's failure to recognise that Rofil was being implanted in the UK, hence its decision to not issue a warning to the UK health system about the Rofil-rebranding of PIP implants. Dutch agency IGZ issued a warning about Rofil in April 2010 (www.clinica.co.uk, 18 August 2010).

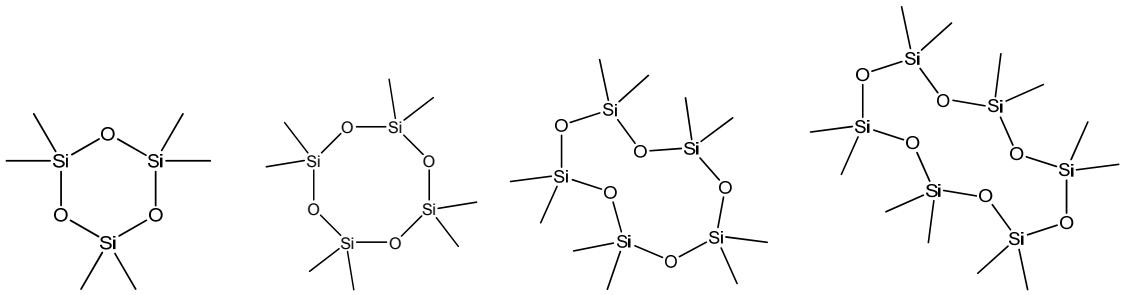
The lack of awareness – not just at the MHRA, but also apparently across the entire UK cosmetic surgery sector – that Rofil implants of any sort were on the UK market helps explain the contrast between the UK and Portuguese responses to the IGZ warning. As Infarmed has since explained, its actions were in response to the realisation that the Rofil brand was on the market, even though the fraudulent rebranded PIP implants specifically are not known to have been distributed there.

Cyclosiloxanes

Materials for the December 4-5, 2008 Meeting of the California Environmental Contaminant Biomonitoring Program (CECBP) Scientific Guidance Panel (SGP)

Agenda Item: "Consideration of Potential Designated Chemicals"

The siloxanes are chemicals that have a backbone structure of silicon and oxygen atoms, alternating in occurrence, and have hydrocarbon groups attached to the silicon side chain. In the cyclosiloxanes, the silicon-oxygen atoms are singly bonded and form a ring. Some widely used cyclosiloxanes are: hexamethylcyclotrisiloxane (D3), octamethylcyclotetrasiloxane (D4), decamethylcyclopentasiloxane (D5) and dodecamethylcyclohexasiloxane (D6).



D3 D4 D5 D6

The cyclosiloxanes are used in the manufacture of silicones, in combination or alone in personal care products, and as carriers, lubricants and solvents in a variety of commercial applications. They occur in environmental media, especially in sewage sludge. In studies conducted by the Nordic countries, D5 was the dominant siloxane in all environmental matrices sampled except for air, where D4 dominated. Certain siloxanes are persistent in the environment, resisting oxidation, reduction, and photodegradation. Varying information exists on the susceptibility of siloxanes to hydrolysis. Some will be metabolized and the metabolites (hydroxylation metabolites) are expected to be found in blood and urine.

Because cyclosiloxanes are ubiquitous, special care is required to avoid the risk of contamination of samples during sample collection, storage and analysis. Evaporation or loss of the volatile siloxanes is also an analytical consideration. D3 is very volatile and subject to analytical difficulties. The necessary equipment to perform the analysis is available in the laboratory; however, method development and standards will be needed.

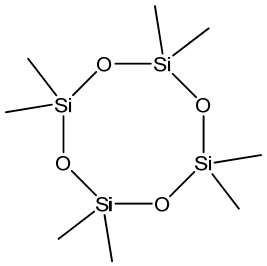
Need to assess efficacy of public health actions:

Cyclosiloxanes appear to be persistent and to have long half-lives in people. The weak estrogenic activity of D4, in combination with its long half-life, poses potential concerns for exposed individuals. While studies have not shown D5 to be estrogenic, it nonetheless increased uterine tumors in animal studies. In addition, there are potential concerns related to effects of D5 on the neurotransmitter dopamine and the hormone prolactin. Cyclosiloxanes are being touted as safer alternatives for a variety of uses, including D5 as a substitute for perchloroethylene in dry

cleaning. It would be important to know if substitutes for existing chemicals are accumulating in the environment. Biomonitoring cyclosiloxanes could detect rising levels in humans, which would be of concern because of the evidence of biological effects associated with these chemicals. These measurements would be an important tool for evaluating the public health efficacy of substituting cyclosiloxanes as less toxic alternatives for other chemicals. This is an especially important question given new efforts under the California Green Chemistry Initiative to encourage the use of safer substitutes.

Additional information on D4, D5 and D6 follows.

Octamethylcyclotetrasiloxane (D4) [CAS No. 556-67-2]



Exposure or potential exposure to the public or specific subgroups:

D4 is an intermediate in the manufacture of polydimethylsiloxanes, which are used in industrial and consumer (personal care and household products) applications including fermentation processes, instant coffee production, paper coatings and sizing, diet soft drinks, waste yeast tanks, food washing solutions, adhesives, textiles, de-asphalting, boiler treatments, detergents, cleaning solutions, surfactants, cosmetic products, and polishes. In combination with D5, D4 is used in the cosmetics and toiletries industry under the trade name cyclomethicone. Annual U.S. import/production volume of D4 was between 100 and 500 million pounds in 2002 (U.S. EPA 2002). D4 has been detected in wastewater streams (Mueller et al. 1995). Human exposures can occur when personal care products, cosmetics and other consumer products containing this substance are used, and potentially could also occur through environmental exposures (HSDB). Horii and Kannan (2008) used measurements of D4 in consumer products to estimate the daily exposure rate for women in the United Sates (ages 19-65) to D4 from the use of personal-care products as approximately 1 milligram (mg)/day.

Known or suspected health effects:

D4 animal toxicity studies found changes in organ weights (Burns-Naas et al. 2002, McKim et al. 2001a, He et al. 2003), induction of hepatic drug metabolizing enzymes (McKim et al. 1998), and adverse effects on reproductive health and function, including weak estrogenic effects (Stump et al. 1997 and 1999, He et al. 2003, Quinn et al. 2007a and 2007b, Siddiqui et al. 2007, Meeks et al. 2007; McKim et al. 2001b). D4 exposure has also been associated with the development of benign uterine tumors (adenomas) in rats (Plotzke et al. 2000). The acute LD50 of 6-7 g/kg indicates that D4 is acutely non-toxic (Lieberman et al. 1999).

Potential to biomonitor:

Physical and chemical properties:

Vapor pressure: 1.05 mmHg at 25 °C.

Water solubility: 5.0×10^{-3} mg/L (5 ppm) at 25 °C.

Octanol/water partition coefficient: Log K_{ow} 5.1

Bioaccumulation: Bioconcentration factor (BCF) 12,400 L/kg

Persistence: Atmospheric degradation $t_{1/2}$ 13 days. Virtually no mobility in soil (K_{oc} 14,000) but some volatilization from moist and dry soil surfaces expected. If released into water, D4adsorbs to suspended solids and sediment and estimated volatilization $t_{1/2}$ 1.8 hours (river); 6.8 days (lake); 120 days (pond).

Past biomonitoring studies: The national survey of human adipose tissue conducted in 1982 analyzed 46 composite samples and qualitatively found D4 in 21 samples (U.S. EPA. 1987). Flassbeck et al. (2001) analyzed plasma and blood of women exposed to silicone gel filled implants (n = 14) and found that many years after the removal of ruptured silicone implants, D4 was present in the range of 14-50 ng/mL in plasma and 79-92 nanograms/milliliter (ng/mL) in blood. D4 was not detectable in plasma or blood of women without implants. In 3 women with silicone gel-filled implants, D4 was the most abundant siloxane found and was present at levels ranging from 11.9 - 1,300 nanograms/gram (ng/g) depending on the woman and the type of tissue sampled; no siloxanes were detected in control breast tissue samples (Flassbeck et al. 2003).

Availability of analytical methods: Hexane is used for extraction. The clear layer of the extract may be ready for High Resolution GC/ High Resolution MS (HRGC/HRMS). Metabolite analysis may be important. Several studies have measured cyclic siloxanes in human and rodent tissues, using gas chromatography coupled with an atomic emission detector (GC-AED) or mass spectrometric detector (GC-MS) (Kala et al. 1997; Flassbeck et al. 2001, 2003; Lykissa et al. 1997).

Availability of adequate biospecimens: Plasma and blood specimens. Highly lipophilic, metabolized by the liver, eliminated by exhalation and excretion – rates depend on the route of exposure (He et al. 2003). Major metabolites in rodents are dimethylsilanediol and methylsilanetriol (Varaprath et al. 1999, 2000).

Incremental analytical cost: Can be bundled with other cyclosiloxanes.

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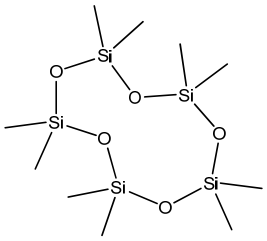
Decamethylcyclopentasiloxane (D5) [CAS No. 541-02-6]



Exposure or potential exposure to the public or specific subgroups:

D5 is used for industrial applications (silicone fluids and elastomers) and in a wide range of consumer products (cosmetics and toiletries). D5 is used as a dry cleaning agent, and has been marketed as a safer alternative to perchloroethylene. In combination with D4, D5 is used in the cosmetics and toiletries industry under the trade name cyclomethicone. U.S. production/import volume of D5 was between 100 and 500 million pounds in 2002 (U.S. EPA 2002). D5 has been detected in indoor and outdoor air (U.S. EPA 1992), in drinking water (Lucas 1984), in sediment (Norden 2005), and in emissions from urethane cushions (Shaeffer et al. 1996). D5 has also been detected in fish and other aquatic organisms (Mait 2005, Norden 2005). Horii and Kannan (2008) estimated total daily exposure to D5 from personal-care and consumer products in women (ages 19-65) in the United States as 233 milligrams (mg)/day.

Known or suspected health effects[1]:

D5 has been shown to cause uterine endometrial adenocarcinomas in female rats (Dow Corning, 2005). D5 also has adverse health effects on the reproductive system, adipose tissue, bile production, and the immune system through its effects on prolactin, and it has the potential to cause adverse effects on the nervous system because of its influence on the neurotransmitter dopamine (OEHHA 2007). In contrast to D4, D5 has not been shown to have estrogenic effects (OEHHA 2007).

Potential to biomonitor:

Physical and chemical properties:

Water solubility 0.017 – 0.05 mg/L at 25°C.

Vapor pressure 0.2 torr (mm Hg) at 25°C.

Octanol/water partition coefficient: Log K_{ow} = 5.2 – 5.71.

Bioaccumulation: Bioconcentration factor (BCF), bioaccumulation factor > 5,000 (Environment Canada 2007).

Persistence: D5 partitions into air, water, soil, and sediment, but mostly ends up in soil and sediment (Environment Canada, 2007). D5 half-life in air is 6.9 days (Atkinson 1989). The probability that D5 will biodegrade in water or soil is "essentially zero" according to Environment Canada (2007). An environmental monitoring study in Nordic countries found D5 to be the dominant cyclosiloxane in fish livers and marine mammals (Norden 2005). Animal experiments have shown that unchanged D5 is persistent in a "variety of tissues" for "extended periods of time;" the half-life in humans is measured in weeks, and "D5 may take a year to reach

[1] Summarized from 2007 OEHHA toxicity data review on D5

steady state in fat tissue" (OEHHA 2007). OEHHA (2007) concluded that D5 "could accumulate in the environment, may bioconcentrate, and is a persistent substance." Environment Canada (2007) concluded that D5 meets the persistence criteria for soils, sediments, and water.[2]

Past biomonitoring studies: A 1982 national survey of human adipose tissue found D5 in 28 of 46 people sampled (U.S. EPA 1987). Kaj et al. (2005) detected D5 levels as high as 4.5 micrograms/liter (µg/L) in human breast milk samples in Sweden. Flassbeck et al. (2001) showed an increase in the amount of low molecular weight cyclic siloxanes in blood of women with silicone breast implants, even several years after the removal of ruptured silicone implants [D5 28 ng/ml detected in one patient]. D5 was not detectable in plasma or blood of women without implants. Flassbeck et al. (2003) found levels of D5 as high as 637±100 ng/g (~637 ppb) in the fat tissue of one woman who had a silicone gel-filled breast implant; no siloxanes were detected in control breast tissue samples.

Availability of analytical methods: Hexane is used for extraction. The clear layer of the extract may be ready for High Resolution GC/ High Resolution MS (HRGC/HRMS) to test for the parent compound which has been detected in human adipose tissue and breast milk.

Availability of adequate biospecimens: Plasma and blood. The metabolites in rat urine are methyl dimethylsilanediol [$Me_2Si(OH)_2$] and methylsilanetriol [$MeSi(OH)_3$] (Varaprath et al. 1999). No human data reported.

Incremental analytical cost: Can be bundled with other cyclosiloxanes.

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Horii Y. and Kannan K. 2008. Survey of organosilicone compounds, including cyclic and linear siloxanes, in personal-care and household products. Arch Environ Contam Toxicol. Apr 29. [Epub ahead of print]..

[2] As set out in the 2000 Government of Canada Persistence and Bioaccumulation Regulations.

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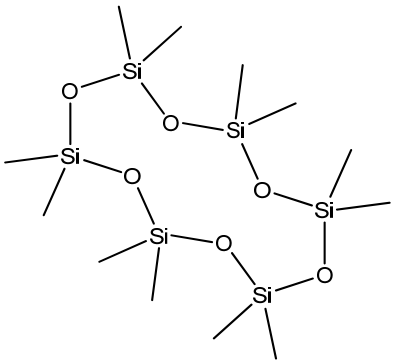
U.S. Environmental Protection Agency (U.S. EPA). 1992. Thirtieth report of the Interagency Agency Testing committee to the Administrator, receipt of report and request for comments regarding Priority Testing List of chemicals. July 9, 1992. Federal Register. 57(132):30603-30618. Available at: http://tsca-itc.syrres.com/itcrep/docs/30.pdf.

U.S. Environmental Protection Agency (U.S. EPA, 2002). Non-Confidential Inventory Update Reporting Production Volume Information. Toxic Substances Control Act (TSCA) Inventory. Available at: http://www.epa.gov/oppt/iur/tools/data/2002-vol.htm.

Dodecamethylcyclohexasiloxane (D6) [CASRN: 540-97-6][3]



Exposure or potential exposure to the public or specific subgroups:

D6 is used in the production of consumer products and industrial products both as a raw material and as an intermediate in the production of silicone polymers. Silicone polymers are used to produce personal care products, pharmaceuticals, defoamers, surfactants, leveling agents, mold release agents, lubricants, cleaners, sealants, architectural coatings, mechanical, heat transfer and dielectric fluids, polishes and coatings. Annual U.S. production/import volume of D6 was between 10 and 50 million pounds in 2002 (U.S. EPA 2002). D6 has been detected in indoor and outdoor air (Kaj et al. 2005, Norden 2005), in drinking water (Lucas 1984), and in sewage sludge (Kaj et al. 2005, Norden 2005). Daily intake of D6 from a variety of sources was estimated by Environment Canada (2008) as ranging from 28.7 µg/kg bodyweight for persons 60 years and older to 87.0 µg/kg bodyweight for children 6 months to 4 years of age. Environment Canada (2008) estimated the upper limit of daily systemic dose of D6 from personal care products to be 100 µg/kg/body weight/day. Horii and Kannan (2008) measured the concentration of D6 in select consumer products (range 0.33 to 43,100 µg/g) and estimated daily exposure for women in the United Sates (ages 19-65) as 22,000 µg/day.

Known or suspected health effects[4]:

The liver is thought to be the target organ for oral exposures, and potentially for inhalation exposures (Environment Canada 2008). D6 exposure has been associated with liver and thyroid enlargement and reproductive effects (Dow Corning 2006). Model calculations suggest that D6 has the potential to affect aquatic organisms at concentrations close to its water solubility (Environment Canada 2008).

Potential to biomonitor:

Physical and chemical properties:

Vapor pressure 4 Pascal (0.03 mm Hg) at 25ºC.
Water solubility 0.00513 mg/L at 23ºC.
Octanol/water partition coefficient: log K_{ow} 4.36-9.06

[3] D6 is also contained under another CAS No. (69430-24-6) which is associated with the following names: cyclopolydimethylsiloxane, cyclopolydimethylsiloxane (DX), cyclosiloxanes di-Me, dimethylcyclopolysiloxane, polydimethyl siloxy cyclics, polydimethylcyclosiloxane, cyclomethicone and mixed cyclosiloxane (Environment Canada 2008).
[4] Summarized from 2008 Environment Canada review of D6

Bioaccumulation: Bioconcentration Factor/Bioaccumulation Factor (BAF/BCF) > 5000. Persistence: In comparison to D4 and D5, D6 has reduced aquatic bioavailability (Environment Canada 2008). The main environmental release of D6 is to air (78 percent) where most (99 percent) of it will remain ($t_{1/2}$ 6 days); of the D6 that ends up in water ($t_{1/2}$ > 180 days), 98 percent is adsorbed to suspended solids (sediment $t_{1/2}$ > 365 days). Almost 100 percent of the D6 that is released to soil remains in soil (soil $t_{1/2}$ > 180days) (Allen et al. 1997, Environment Canada 2008). Environment Canada (2008) concluded that with a biomagnification factor (BMF) of 20, D6 is "likely to biomagnify in terrestrial food chains." It also concluded that D6 meets the criteria for persistence and bioaccumulation potential in air, water, and sediment.[5]

Past biomonitoring studies: A 1982 national survey of human adipose tissue found D6 in 28 of 46 people sampled (U.S. EPA 1987). Flassbeck et al. (2001) analyzed plasma and blood of women exposed to silicone gel filled implants (n = 14) and found that many years after the removal of ruptured silicone implants, D6 was present (17 ng/mL, ~ 17 ppb) in the plasma of one woman. D6 was not detectable in plasma or blood of women without implants. In 3 women with silicone gel-filled implants, D6 was present at levels ranging from 25.1-780 ng/g (~25-780 ppb) depending on the woman and the type of tissue sampled; no siloxanes were detected in control breast tissue samples (Flassbeck et al. 2003).

Availability of analytical methods: Method similar to those used for analyzing D4 and D5.

Availability of adequate biospecimens: Plasma and blood.

Incremental analytical cost: Can be bundled with other cyclosiloxanes.

References:

Allen RB, Kochs P, Chandra G. 1997. Industrial organic materials, their environmental entry and predicted fate. In G. Chandra, Editor, The Handbook of Environmental Chemistry, Part H: Organosilicon Materials vol. 3, Springer-Verlag, Berlin. pp. 1-25.

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5 As set out in the 2000 Government of Canada Persistence and Bioaccumulation Regulations.

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Horii Y. and Kannan K. 2008. Survey of organosilicone compounds, including cyclic and linear siloxanes, in personal-care and household products. Arch Environ Contam Toxicol. 55(4):701-710.

Kaj L, Andersson J, Palm Cousins A, Remberger M, Ekheden Y, Dusan B, and Brorström-Lundén E. 2005. Results from the Swedish National Screening Programme 2004: Subreport 4:Siloxanes. IVL Swedish Environmental Research Institute.

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[NILU] Norsk institutt for luftforskning. 2007. Siloxanes in the environment of the Inner Oslo fjord. Rapport 986/2007. Available at: http://www.nilu.no/data/inc/leverfil.cfm?id=23299&type=6.

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OEHHA Toxicity Data Review: Decamethylcyclopentasiloxane (D5). September 13, 2007. Available at: http://www.arb.ca.gov/toxics/dryclean/oehhad5review.pdf.

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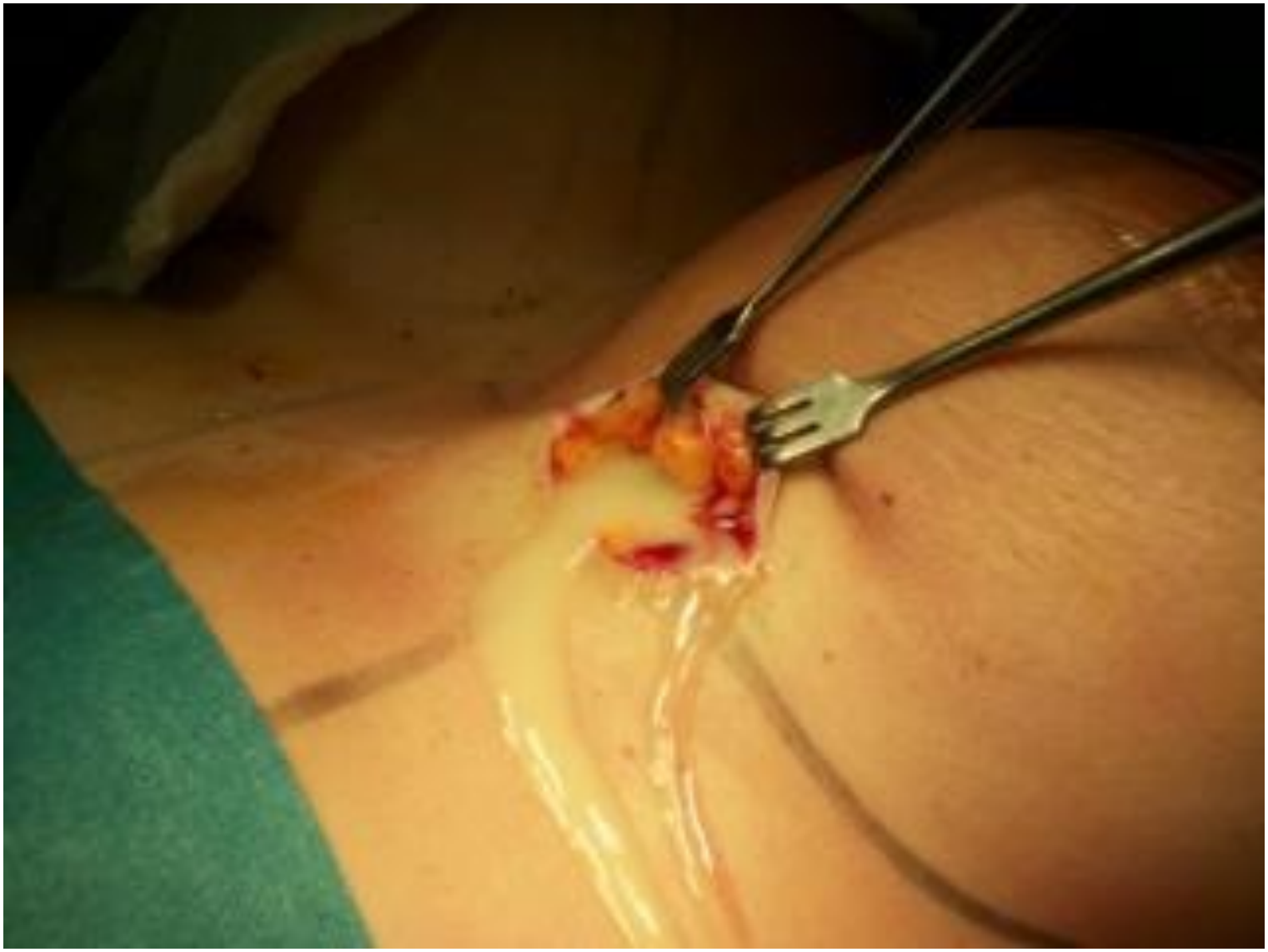

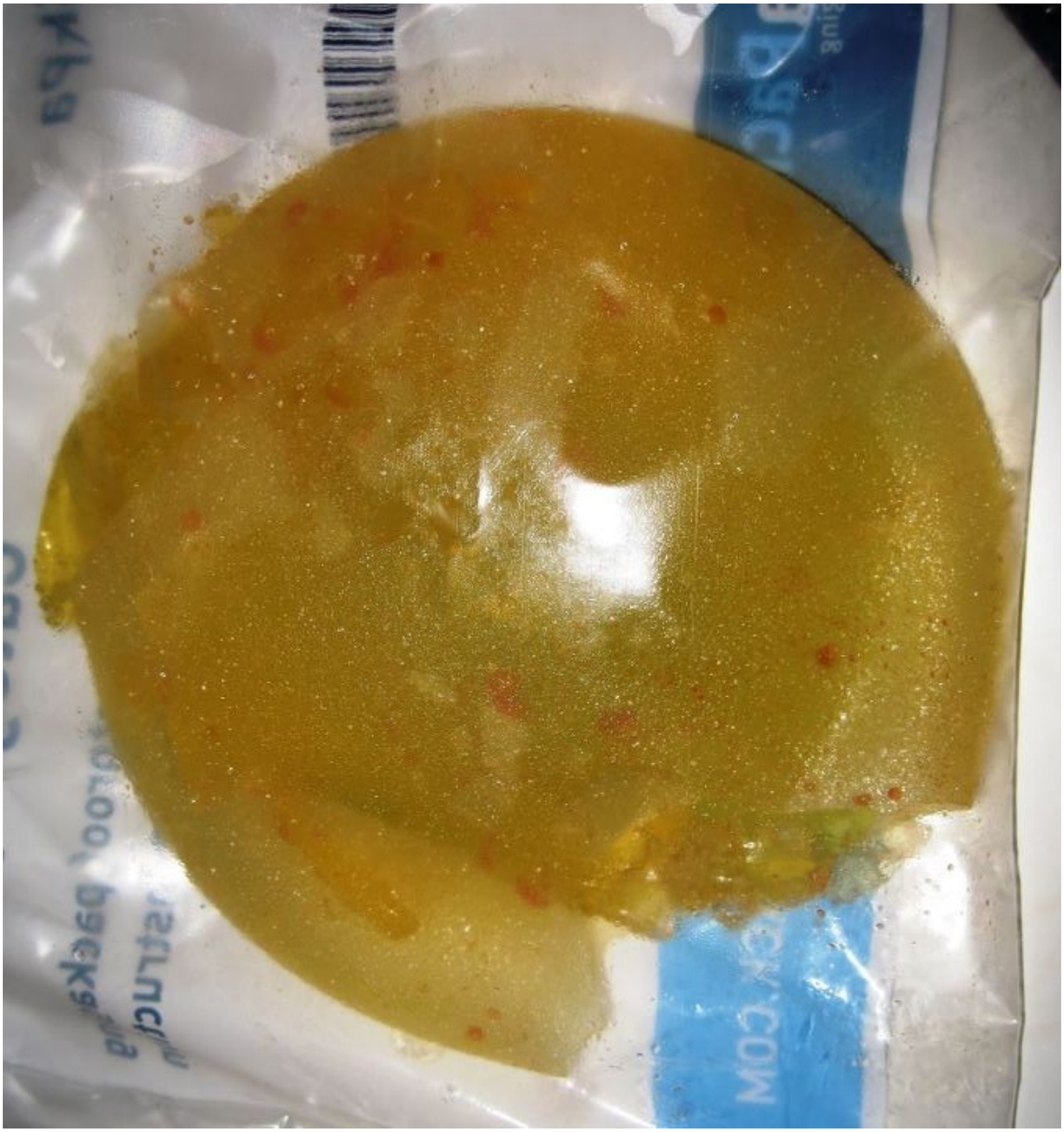

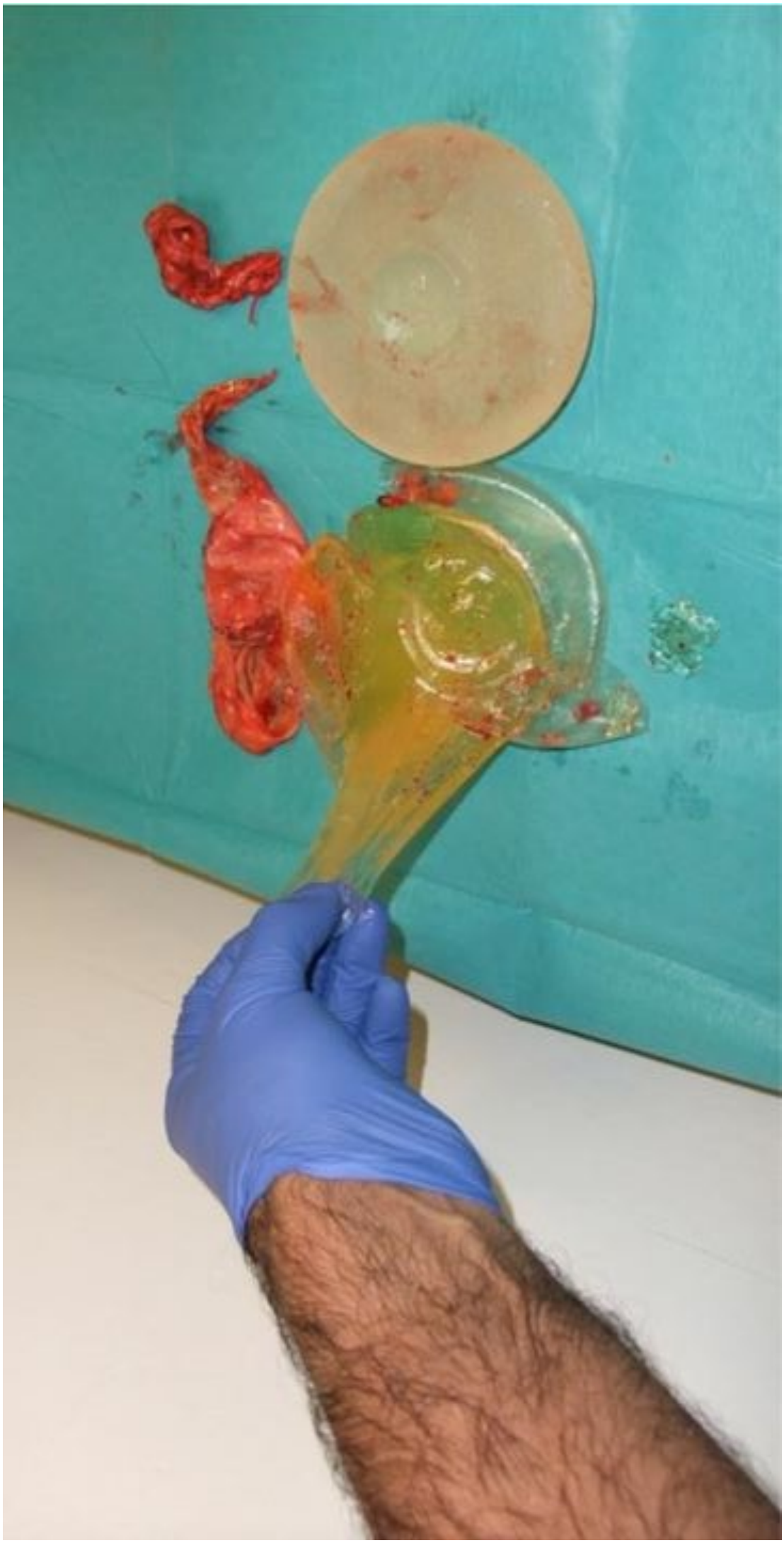

Scientific Committee on Emerging and Newly Identified Health Risks

SCENIHR

The Safety of PIP Silicone Breast Implants

Version of 1st February 2012

SCENIHR adopted this opinion by written procedure on 1st February 2012

About the Scientific Committees

Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

They are: the Scientific Committee on Consumer Safety (SCCS), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) and are made up of external experts.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Agency (EMA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCENIHR

This Committee deals with questions related to emerging or newly identified health and environmental risks and on broad, complex or multidisciplinary issues requiring a comprehensive assessment of risks to consumer safety or public health and related issues not covered by other Community risk assessment bodies. Examples of potential areas of activity include potential risks associated with interaction of risk factors, synergic effects, cumulative effects, antimicrobial resistance, new technologies such as nanotechnologies, medical devices including those incorporating substances of animal and/or human origin, tissue engineering, blood products, fertility reduction, cancer of endocrine organs, physical hazards such as noise and electromagnetic fields (from mobile phones, transmitters and electronically controlled home environments), and methodologies for assessing new risks. It may also be invited to address risks related to public health determinants and non-transmissible diseases.

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All Declarations of working group members and supporting experts are available at the following webpage:

http://ec.europa.eu/health/scientific_committees/emerging/members_committee/index_en.htm

ABSTRACT

Breast implants can fail, regardless of manufacturer, and the probability of failure increases with time since implantation. This phenomenon is true for all types of implants used in humans. In most cases, breast implant failure appears to be without identifiable health consequences for the patient with the exception of possible local complications.

The question asked of the SCENIHR is: Are the breast implants manufactured by PIP more prone to failure than those of other manufacturers, and what are the consequences to health, if any, from PIP implant failures?

In view of the nature and reliability of the available data on breast implants overall and the urgency of an Opinion from the SCENIHR on PIP silicone breast implants in particular, the focus of attention in this initial response is on the following aspects:

- Physical and chemical properties of the PIP silicone breast implants, where accessible;

- Findings of the effects of PIP implant contents in the required safety tests, where available;

- Reports of incidents of PIP implant failures, where available.

It should be noted that PIP silicone breast implants have been found to vary considerably in composition and, as a result they are likely to vary substantially in performance characteristics. No clear temporal trend of implant problems has been identified for PIP silicone breast implants. Consequently it is very difficult to identify a truly representative PIP implant for testing purposes.

i) Physical and chemical properties

The available evidence indicates that many PIP silicone breast implants were manufactured from industrial grade silicone of lower quality than medical grade silicone. This appears to be associated with a higher content of low molecular weight components. As a consequence of the migration of these components it is reasonable to conclude that the shell might be weakened and that components could leak into the surrounding tissue. Tests conducted by the French Authorities on the physical integrity of a sample of PIP silicone breast implants indicated weaknesses in PIP shells not found in other commercially available implants.

ii) Toxicity tests findings

To date, few studies aimed at evaluating the toxicity of the contents of PIP silicone breast implants have been conducted using the tests specified for assessing the safety of Class III medical devices (which includes breast implants). The tests that were performed are designed to assess cytotoxicity, irritancy and genotoxicity. Medical grade silicone gels used in other breast implants gave negative results in these tests.

In the case of the contents of the PIP silicone breast implants, tests for cytotoxicity and genotoxicity were negative. However, an *in vivo* test for irritancy was positive. This indicates the potential for inducing local irritancy (which may manifest as sore and/or enlarged local lymph nodes or sensation in the breast) when the silicone gel is released from the implant. The form that local irritancy might take will depend on the amount released, the duration of exposure and other local conditions. The implications of this positive result in an irritancy test, for women with PIP silicone breast implants are currently uncertain and further investigation is required.

iii) Incident reports

It is important to note that clinical breast examinations alone have little sensitivity for detecting implant rupture. If there are clinical signs of adverse effects, then a diagnostic work-up is mandatory.

There are cases reported suggesting that PIP silicone breast implants may have a higher failure rate in the first few years after implantation compared with those from other breast implant manufacturers. There are also a few case reports that ruptured PIP

silicone breast implants may be associated with a higher incidence of swollen and painful lymph nodes in the axilla, the groin, the neck and the mediastinum.

The limited clinical data, along with the absence of epidemiologic data on PIP silicone breast implants provide insufficient evidence to warrant a conclusion that women with PIP silicone breast implants have a greater risk to their health than women with breast implants from other manufacturers. In regard to breast implants in general there is, , a reasonable number of large, good-quality studies showing no increase in any cancer type or connective tissue disease among women with standard silicone breast implants (including women with ruptured implants). However, in the case of PIP implants, when the limited available clinical information is taken together with the findings from tests of the physical and chemical properties of the shell and silicone, and of the *in vivo* irritancy test, some concerns are raised about the safety of PIP silicone such breast implants as the possibility for health effects cannot be ruled out.

Further work is proposed to establish with greater certainty the health risks, if any, that may be associated with PIP silicone breast implants.

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

Opinion to be cited as:

SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks), Safety of PIP Silicone Breast Implant, 1 February 2012

TABLE OF CONTENTS

EXECUTIVE SUMMARY

1) The SCENIHR has been asked to address the potential risks from PIP breast implants because, according to the findings of the French Health Authorities, the French manufacturer (Poly Implant Prothèse; abbreviated as "PIP") made use of low-quality material (industrial silicone). In such an assessment, it is important to compare the available information with findings for breast implants from other manufacturers.

2) Important difficulties in making such an assessment are:

   a) The number of patients in the individual member states is unknown due to patient tourism and poor record keeping by the manufacturers of PIP silicone breast implants;

   b) Reporting of breast implant failure and of related adverse effects on health is not obligatory. Consequently, reported incident rates are unreliable. However, even for silicone implants of standard quality, reoperations are needed eventually for a high number of patients.

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

4) There are various methods to identify implant failure. It is important to note that clinical breast examinations alone have little sensitivity for detecting implant rupture. If there are clinical signs of adverse effects, then a diagnostic work-up is mandatory. A clinical examination is therefore likely to miss implant rupture in the absence of positive signs. There is international agreement among professional radiologists and reconstructive and aesthetic surgeons that Magnetic Resonance Imaging (MRI) is the most accurate modality to detect ruptures. A meta-analysis has estimated the overall sensitivity to 78% (95% CI, 71%-83%) and the overall specificity was 91% (95% CI, 86%-94%). Ultrasonography is the second best imaging modality for detecting ruptures. However, ultrasonography is less precise and more dependent on the human operator than MRI. Mammography is even less useful.

5) Silicone breast implants can fail, regardless of manufacturer, and the probability of failure increases with time since implantation. This phenomenon is true for all the types of implants used in the human body. Most breast implants seem to be rather durable for the first 6-8 years, whereafter the risk of rupture increases. For third generation implants a general rupture risk 10%–15% within 10 years of implantation seems to be an appropriate estimate. Implants with more cohesive silicone seem to have lower risk of rupture.

6) The reported frequency of local complications among silicone breast implant recipients generally ranges between 17% and 36%. Additional surgery after primary implantation as a result of these complications has been reported to range from 10 to 30%. Capsular contracture is the most frequent reason for additional surgery in women with breast implants with frequencies ranging from 2% to 23% in recent reports. Other complications include pain, haematoma and infection.

7) Other possible healths effects of silicone breast implants that have been investigated in epidemiological studies include:

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

   b) ALCL: A very rare type of lymphoma, the Anaplastic Large Cell Lymphoma (ALCL) has been found in the scar capsular tissue around breast implants in 60 patients globally. According to the US Food and Drug Administration (FDA), there might be a minimally increased risk to develop this tumour for patients with breast implants.

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

d) Connective Tissue Diseases (CTDs): Although there were initial reports of associations with various forms of connective tissue disease, subsequent, large-scale epidemiologic investigations provided consistent evidence against these claims.

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

f) Immunological effects: Occasionally foreign body reactions have been reported in a small number of women with breast implants.

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

8) The risk factors for breast implant failure may be identified as:

a) Physical and chemical features of the implant;

b) The implantation procedure;

c) Time since the implantation;

d) Patient specific factors, *e.g.*, accidents.

9) This Opinion draws on three sources of data, namely,

a) An extensive search of the published literature;

b) Information provided by some Member States, in particular France, and other national authorities;

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

Because of the urgency of a Scientific Opinion from the SCENIHR, the Committee could only consider the readily available data. The SCENHIR is aware that PIP silicone breast implants have been found to vary considerably in composition and, as a result, are likely to vary substantially in performance characteristics. No clear temporal trend of implant problems has been identified for PIP silicone breast implants. Consequently, it is very difficult to identify a truly representative PIP implant for risk assessment purposes.

10) The data available on PIP are inevitably limited at this stage. The focus of attention in this initial response is on the following aspects:

a) Physical and chemical properties of the PIP silicone breast implants, where available;

b) Findings of the effects of PIP implant contents in some required safety tests, where available;

c) Reports of incidents of PIP implant failures, where available.

11) Physical and chemical properties: The more recent PIP silicone breast implants in common with those of other manufacturers comprise a single envelope/shell. The implants consist of an outer highly cross linked elastomer shell filled with a gel withmore limited cross linking. In common with those of most other manufacturers,

PIP silicone breast implants were manufactured using the polymer polydimethylsiloxane, also known as silicone. The chemical reaction resulting in gel formation must be controlled because it governs the degree of crosslinking. The more variable this reaction is the greater is the variation of the content of volatile and/or low molecular mass components in the implant (gel and shell). Use of industrial grade silicone, along with a lesser control of the cross linking process, appears to be associated with a higher content of low molecular weight components in PIP silicone breast implants. As a consequence of the migration of these components, it is reasonable to conclude that the shell might be weakened and that components could leak into the surrounding tissue. Tests conducted by the French Authorities on the physical integrity of a sample of PIP silicone breast implants indicated weaknesses in PIP shells not found in other commercially available implants.

12) Findings in Toxicity tests: A range of assays are available for toxicity testing. For implant devices with which there will be prolonged contact with the patient the most extensive toxicity testing is needed with end-points including cytotoxicity, sensitization, irritation, acute and subchronic systemic toxicity, genotoxicity, and implantation tests. Additional tests may be indicated by the risk assessment that is performed of a certain medical device/constituent and these may include biodegradation and toxicokinetic studies, chronic toxicity, carcinogenicity, immunotoxicity, neurotoxicity and reproductive/developmental toxicity. To date few studies aimed at evaluating the toxicity of the contents of PIP silicone breast implants have been conducted using tests specified for assessing the safety of Class III medical devices. The tests that have been performed are designed to assess cytotoxicity, irritancy and genotoxicity. Medical grade silicone gels gave negative results in these tests. In the case of the contents of the PIP silicone breast implants, tests for cytotoxicity and genotoxicity were negative. However, an *in vivo* test for irritancy was positive. This indicates the potential for inducing local irritancy when the silicone gel is released from the implant. Any effects will depend on the amount released, the duration of exposure and other local conditions. The implications of this positive irritancy test result for women with PIP silicone breast implants are currently uncertain and further investigation is required.

13) Incident reports: There are cases reported suggesting that PIP silicone breast implants may have a higher failure rate in the first few years after implantation compared with those from other breast implant manufacturers. There are also case reports indicating that PIP silicone breast implants may be associated with a higher incidence of swollen and painful lymph nodes not only in the axilla but also in the neck, the groin and the mediastinum, after rupture but sometimes even without rupture.

    The limited and selective clinical data along with the absence of epidemiologic data specifically on the PIP silicone breast implants provide insufficient evidence to warrant a conclusion whether these implants pose hazards not identifed among women with implants of standard quality. In particular, the data preclude a conclusion whether women with PIP silicone breast implants have greater risks to their health than women with breast implants from other manufacturers. However, when the limited available information is taken together with the findings from tests of the physical and chemical properties of the shell and silicone, and of the in vivo irritancy test, some concerns are raised about the safety of PIP silicone breast implants. The possibility for health effects cannot be ruled out.

14) The SCENIHR is asked to identify the generic risks and benefits of various actions that might be taken to address these concerns. As noted above there are obvious difficulties in providing scientifically based advice because:

    a) Regardless of the manufacturer, the failure rate of an implant increases over time;

b) For many women, it is uncertain whether their breast implant is a PIP manufactured implant;

c) Simple clinical examination alone is unlikely to identify those patients with a leaking/ruptured implant.

d) Many PIP silicone breast implants have been inserted by surgeons who are not qualified in plastic surgery. This might be a source of higher failure rates among their patients.

15) It is important to identify, as far as possible, high-risk categories of patients based on the identified risk factors noted above. Key factors including manufacturer, duration of implant in the body of the patient, patient symptoms, and psychological state have been identified. However, these criteria are insufficiently established at present as regards PIP silicone breast implants and a patient-by-patient approach is therefore required. It is important that the potential risks identified in this opinion are considered in the light of the risks involved in prophylactic explantation.

A controlled prophylactic explantation definitely carries less risk than an explantation after rupture or after the onset of symptoms of inflammation and/or lymphadenopathy. Considering the reduced stability of the shell of PIP silicone breast implants, it is possible that the implant will have to be exchanged for most of the women with such implants within the next 10–15 years.

16) The SCENIHR recommends that further work is undertaken as a priority to establish with greater certainty the type and magnitude of health risks, if they exist, associated with PIP silicone breast implants. In particular,

a) A thorough assessment of the chemical composition of a range of PIP silicone breast implants/explants;

b) Further assessment of biological effects of the silicone gel used in PIP silicone breast implants/explants;

c) Further research on PIP explants to identify cause of failure;

d) The development of simple tests that can be used for routine reliable low cost screening to identify ruptures in (PIP) implants;

e) The establishment of a reliable database on Silicone Breast Implant (SBI) and other implant failures and health effects of such failures.

1. BACKGROUND

According to the findings of the French Health Authorities, a French manufacturer (Poly Implant Prothese) fraudulently made use of low-quality material (industrial silicone) different from the one it had declared in the documents submitted for conformity assessment (medical grade silicone).

The company stopped producing breast implants March 2010.

More detailed and regularly updated information can be found on the French authority's websites[1].

The French Health Authorities published recommendations on Friday, 23 December 2011. The French Health Authorities have recommended in particular:

- that any woman implanted with PIP breast implants consult her surgeon;
- the explantation (removal) of the PIP breast implants in case of implant rupture, or suspicion of rupture or oozing.
- that, as a preventive measure, but not as an emergency, the explantation of PIP breast implants is proposed, even in the absence of any clinical sign of implant deterioration.
  For women who refuse explantation, a close medical follow up is recommended;

There is today no common approach in terms of risk management in the different Member States and some Member States have not advised to explant PIP breast implants preventively but to closely monitor women who have received these implants.

It should be noted that during the preparation of this Opinion it became apparent that PIP silicone breast implants were also marketed by another company under the name of M-Implants and Rofil Implant.

[1] http://www.afssaps.fr/ and http://www.sante.gouv.fr

2. TERMS OF REFERENCE

In the light of the above considerations and on the basis of the available scientific evidence, the Scientific Committee on Emerging and Newly Identified Health Risks is requested to provide a rapid scientific opinion on 'The safety of PIP breast implants' according to the provisions of Article 2.3 of Decision 721/2008/EC.

In particular, the SCENIHR is asked:

1. To determine whether implanted PIP breast implants could give reasons for concern from the health point of view when compared with state of the art implants, taking into account their structure, composition and detected defects (*e.g.* low quality silicon, single envelop instead of double envelop) and the risk of rupture and oozing they may present;
2. In case reasons for concern related to implanted PIP breast implants are identified, to make a risk/benefit analysis of explantation.

In its assessment the SCENIHR is invited to take into account in particular:

- the global reported incident rate associated with PIP breast implants;
- the comparison of this global reported incident rate compared with other breast implants;
- the percentage of this global reported incident rate associated with rupture of PIP breast implants;
- the percentage of this global reported incident rate associated with other type of problems (*e.g.*, inflammatory reactions);
- any evidence suggesting that PIP breast implants are more difficult to explant, before or after rupture, in comparison with other breast implants;
- any increased report of lymph node complications associated with the PIP breast implants.

3. BREAST IMPLANTS GENERAL CONSIDERATIONS

3.1. Introduction and background

Breast implants are considered medical devices and as such are subject to both a preclinical and clinical evaluation before market approval is granted. This section provides an overview on the regulatory framework for medical devices and more specifically for breast implants. In addition the history in the use of breast implants is presented.

3.2. Regulatory framework for medical devices

The EU regulatory framework for medical devices is built on three main Directives:

- Council Directive 90/385/EEC2 on the approximation of laws of the Member States relating to active implantable medical devices (hereafter AIMDD),
- Council Directive 93/42/EEC3 concerning medical devices (hereafter MDD), and
- Directive 98/79/EC4 of the European Parliament and of the Council on in vitro diagnostic medical devices (hereafter IVDD).

The key elements of this regulatory framework are detailed below.

Manufacturers shall ensure that the devices they place on the market comply with the legal requirements and do not compromise the health or safety of patients and users.

Before placing them on the market, manufacturers must carry out an assessment of the conformity of their devices. For devices of medium and high risk, the intervention of a third party conformity assessment body, so-called notified body, is compulsory in the conformity assessment before the placing on the market of the device to verify that it fulfils the relevant legal requirements, in particular the applicable essential requirements laid down in the legislation. Breast implants are in the highest risk class (*i.e.*, class III) since 2003[5]6 and as such are submitted to the most stringent pre-market review. In particular, the notified body is required to examine either the design dossier regarding the device or a type of a device. Moreover, it must audit the Quality System to ensure that the manufacturer produces devices which conform to the approved design or type. The notified body must periodically carry out appropriate inspections and assessments to make sure that the manufacturer applies the approved quality system. The notified body may pay also unannounced visits to the manufacturer. At the time of a visit, the notified body may, where necessary, carry out or ask for tests in order to check that the quality system is working properly.

Once devices are on the market, manufacturers must notify the relevant national Competent Authority about incidents and shall investigate these incidents and take any corrective action necessary. National competent authorities need to follow specific procedures laid down in the legislation when they consider that an unsafe medical device must be withdrawn from the market ("safeguard clause") or when a CE marking is unjustifiably affixed to a device or missing ("wrongly affixed CE marking").

[2] OJ L 189, 20.7.1990, p. 17
[3] OJ L 169, 12.7.1993, p. 1
[4] OJ L 331, 7.12.1998, p. 1
[5] OJ L 28/43, 4.2.2003, p. 43

3.3. Procedure related to CE marking on breast implants

Before affixing the CE marking on a breast implant, the manufacturer must follow a conformity assessment procedure where a notified body intervenes to check the conformity of the product with the applicable essential requirements.

In order to show conformity with the essential requirements a safety evaluation on breast implant materials has to be performed. The safety evaluation should be performed within the context of a risk management process such as described in the international standard EN ISO 14971 for the application of risk management to medical devices (EN ISO 14971: 2009). To minimize the risks involved in the use of the device, all known or foreseeable hazards should be identified, and the risks arising from the identified hazards should be estimated and evaluated. The risks should be controlled by eliminating or reducing them as far as possible, aiming for inherent safety by design. This should be an iterative process incorporating information becoming available from clinical use and post marketing surveillance.

Specific product standards dealing with implants in general and breast implants in particular exist describing specific requirements and testing. General requirements described in EN ISO 14630 (EN ISO 14630:2008 Non active surgical implants – general requirements) include aspects on performance, design, materials, design evaluation, manufacture, sterilization, packaging and information supplied by the manufacturer, Specific requirements for breast impants related to the issues mentioned above are described in EN ISO 14607 (EN ISO 14607; 2007 Non active surgical implants – mammary implants – particular requirements). In this standard the preclinical evaluation of breast implants includes mechanical tests including shell integrity (elongation, tear resistance, strength of joints, seams or seals, and design of shell), valve or injection site competence, filling material (compatibility between filling material and shell, test for silicone gel cohesion), implant resistance (static rupture resistance testing, fatigue resistance testing and impact resistance), volume, dimensions, and surface. In addition, chemical evaluation needs to be done including testing of shell material, silicone elastomer or coated materials, filler materials, and a release test. Furthermore a biological evaluation needs to be performed in accordance with EN ISO 10993-1, and a clinical evaluation in accordance with EN ISO 14155. The biological evaluation is elaborated in section 5.2.

3.2 Brief history of breast implants

3.4.1 Implants in general

Silicone breast implants (SBI) were introduced in 1963 in the United States and soon spread to the rest of the western world. For years, the only available types of implants contained silicone membranes and fillings. Later, saline was introduced as a filler, and certain other substances have been tried, but various drawbacks have so far ruled out their widespread use. Breast implants have been modified along the way for improvements on the basis of suggestions by both patients and surgeons (Brody 2009).

There is consensus in the literature to classify implants into generations to indicate certain physical characteristics specific for the types of implants in question. This classification is simplified, but necessary in the scientific literature to compare for instance complications after implant surgery. The most precise grouping into generations would be by characteristics of both the silicone shell/membrane and by the filler silicone (Hölmich *et al.*, 2001). However, since this demands specific information about individual implants, a more practical approach is the categorization according to calendar time. A major confounder is that distributors in different countries have introduced new implant

generations at different calendar time. Some manufactures have produced more than one generation of implants at the same time, and implants can be used for up to 5 years after production (Hölmich *et al.*, 2001).

The initial implants were rather firm both in membrane and gel, the second generation implants were made softer and the membrane less viscous. It became clear that a substantial gel-bleed as well as a high number of ruptures was found in the second generation implants, and modifications were made for improvement, resulting in the subsequent third generation implants. The silicone elastomer was enforced with a barrier layer, which may differ among different products, but the term "low-bleed membrane" or "barrier-coated membrane" is widely used. The gel in third generation implants has again been made somewhat less viscous/ more cohesive. At the same time (about 1989), due to complications with tight scar tissue around implants (capsular contracture), a texturing of the surface was introduced. The third-generation implants, which are still in use, are produced both with a smooth or textured surface (Brody 2009).

High degree of cohesiveness is achieved by increased cross-linking of the polymer silicone gel molecules. This makes the gel firmer, which can be perceived as a disadvantage, however, the implants are more form-stable and anatomical design can be applied, as in the newer, "fourth generation implants". In addition, these implants are considered safer with respect to rupture. The anatomical fourth generation implants were introduced by McGhan in the mid 90's and other companies followed. A "fifth generation" of implants has been introduced with anatomical implants with an even more cohesive gel in the most projecting part of the implant. There is no consensus among manufacturers regarding terminology or classification of cohesiveness, which makes comparisons difficult. Most of the larger companies offer different types of cohesiveness within their repertoire.

For a rupture study, characterisation of implants in a Danish cohort led to the following simplified stratification based on calendar year: First generation implants were used in Denmark in the period 1974–78, second-generation implants in the period 1979–87; and the third-generation barrier-coated, low-bleed implants, which are currently in use, have been available since 1988. The first fourth-generation implants were used in 1994 (Hölmich *et al.*, 2001).

3.4.2 PIP silicone breast implants

The silicone Poly Implant Prosthèses were produced in France since 2001 in its present form. These PIP silicone breast implants have been found to contain an inferior silicone and have not been produced according to the documented procedures provided to obtain CE-mark. They have been available in smooth and textured variants. If classified by calendar time of production and marketing, they would be considered as third generation implants. However, based on reports of a large number of early ruptures, as well as heavy gel bleeds, these implants behave like the older and inferior second generation implants. In addition to the brand name PIP these implants have also been marketed by another company under the name M-implants and Rofil implant.

4. APPROACH USED TO DEVELOP THIS OPINION

This section describes the various methods used to obtain information on the potential risks associated with the use of silicone breast implants in general and PIP breast implants in particular.

4.1 Search on the published literature on silicone breast implants

The European Commission contracted a search on the published literature on silicone breast implants. The search yielded more than 300 hits.

The aim of this work was to carry out a rapid and comprehensive data examination activity related to the subject of PIP silicone implants from 1998 to present. Virtually all of the extensive published literature on breast implants pertains to silicone gel breast implants in general without reference to manufactuerer. These studies include implants of the earliest generation of implants through to the latest, highly cohesive fourth (fifth?) generation implants. Data specifically addressing safety and health effects of PIP silicone breast implants are extremely limited but will be noted where available.

We have included articles from the peer reviewed scientific literature on:

- Occurrence of various diseases and complications in relation to silicone breast implants in general, including potential links with breast cancer, other cancers, connective tissue diseases, offspring effects and other health effects such as inflammation, irritation and infection.
- Rupture of silicone breast implants in general, including rates/frequency, clinical sequelae as well as complications associated with side effects of both intact and ruptured breast implants.
- Toxicological data on silicone breast implants.
- Information on the toxicity, safety and clinical effects of PIP silicone breast implants.
- Occurrence of health effects of implantation/explantation of silicone breast implants, including medical sequelae, infections and inflammations.
- Information on the composition of silicone breast implants and silicone gels, including additives, stabilizers, impurities and by-products.
- Epidemiological and clinical rupture information on silicone implants destined for the buttocks, testicles, lips.

PubMed was the primary search engine used to find articles from the scientific literature published from 1998 to present. The searches carried out are summarised in the table below.

Search term(s)	**Number of articles**
Silicone breast implants	1,025#
Silicone breast implants (review papers)	130
(Silicone breast implants) AND (breast cancer)	232
(Silicone breast implants) AND (rupture)	148
(Silicone breast implants) AND (intact)	36
(Silicone breast implants) AND (inflammation)	94
(Silicone breast implants) AND (infection)	78
(Silicone breast implants) AND (irritation)	0

(Silicone breast implants) AND (epidemiology)	121
(Silicone breast implants) AND (toxicology)	3
(Silicone breast implants) AND (removal)	110
(PIP implants)	110
(PIP implants) NOT (contraceptives)	37
(Silicone implants) AND (buttocks)	22
(Silicone implants) AND (testicles)	8
(Silicone implants) AND (lips)	17
(Silicone implants) AND (composition)	31
(Silicone implants) AND (impurities)	1
(Silicone implants) AND (additives)	3
(Silicone implants) AND (by-products)	1
(Silicone breast implants) and (stabilizers)	1

Article titles only were checked for the search indicated by hash '#' because of the large number of results obtained. The abstracts of all other articles located were checked and there was found to be considerable overlap between the search results.

Lists of potentially relevant articles have been compiled. The titles and bibliographical data for these articles are given in the tables below. Where available, the research group/expert(s), institute or company details have also been included. Articles which examine the following endpoints/effects have been included in the search results and those which fall into more than one category are indicated by an asterisk '*':

* Review papers on silicone breast implants which have been grouped according to the following categories (where the main topic of the review was clear):
    - ° Cancer
    - ° Non-cancer effects
    - ° Rupture
    - ° Other;
* Links between silicone breast implants and breast cancer;
* Inflammation and silicone breast implants;
* Infection and silicone breast implants;
* Rupture of silicone breast implants;
* Intact silicone breast implants;
* Composition of silicone implants;
* Toxicological data on silicone breast implants;
* Epidemiological data on silicone breast implants;
* Removal of silicone breast implants;
* PIP implants; and
* Silicone implants in buttocks, testicles and lips.

Where possible, the full papers of the potentially relevant articles have been retrieved. Abstracts only have been provided for articles which fall into one or more of the following categories:

* Those which are Epub ahead of print;
* In languages other than English;
* Unavailable in PDF format for immediate download from the document supplier.

4.2 Information gathering from plastic and aesthetic surgeons' network

The International Confederation for Plastic Reconstructive and Aesthetic Surgery represents almost all Board Certified plastic surgeons in the world (about 40 000) in 102 nations. It has gathered incident reports from Spain, France, UK, Finland, Lebanon, Cech Republic, Italy and Switzerland. From within this network of fully trained plastic surgeons further information regarding PIP and M-implants could be obtained: It is very difficult to identify which patients received PIP silicone breast implants. M-implants continued to be on the market in Eastern Europe *e.g.* Estonia at least until end of October 2011. Patient tourism is very common with patients from Western European nations travel to Eastern Europe and Thailand for surgery at lower expenses, while patients from the Arab world have their surgery in the Western European nations.

4.3 Data provided by member states and other national authorities

The European Commission formally requested submission of relevant data from the Member States and other national authorities. The call was answered without delay by those Member States and other national authorities having data.

5. PHYSICAL, CHEMICAL AND TOXICOLOGICAL PROPERTIES OF BREAST IMPLANT DEVICES

5.1 Physicochemical nature of breast implant devices

5.1.1 The envelope/shell/membrane

Breast implants consist of an outer shell filled with a gel or liquid solution. Most breast implants are manufactured using the polymer polydimethylsiloxane, also known as silicone. Both the shell and the content (filling material) consist of polydimethylsiloxane the level of cross linking between the polymers determining the fluidness/liquidness of the material. The shell consists of a silicone elastomer with a high level of cross linking between the polymers, whereas the filling of the implants consists of silicone gel with a lower level of cross linking (Williams 1996). In addition, fillers may be present notably amorphous silica in the elastomeric shell to increase the tear resistance. It should be noted that besides breast implant a variety of medical devices are manufactured composed of silicone elastomers.

Most implants comprise a single envelope. This envelope may on occasion have small, difficult to detect pinhole defects. Defects such as tiny cracks are sometimes also found where the posterior patch is 'welded' to the remaining implant.

5.1.2 The contents: Chemical composition and physical properties.

Due to its production method all commercial silicone products will contain some low-molecular-weight species as well as the cross linked macromolecules of the polydimethylsiloxane (Williams 1996). These elastomers can have a variety of molecular sizes. In some breast implants water is used as the filling material.

The degree of crosslinking is influenced by the chemistry of the system used, its stoichiometry and last but not least by the mixing and processing conditions (time and temperatures applied). Additionally, the properties of cross-linked silicones are strongly influenced by the amount and surface properties of the nano-silica filler added for sufficient mechanical properties of the silicone rubber.

Dependant on the chemical reaction during gel formation the degree of crosslinking might vary strongly which results in a strong variation of the content of volatile and/or low molecular mass components in the implant (gel and shell). Therefore, one has not only to consider (strong) variation of mechanical properties (viz. modulus, strength and elongation at break) of the shell but also a much faster release of the unreacted silicone components via the shell into the surrounding tissue. However, the amount of such material released depends on the overall concentration of the low molar mass proportion of the components. Therefore, for example a standard medical grade gel (Nusil MED3-6300, Nusil Technology LLC, Carpinteria, CA, USA) is specified with a volatile content of less than 1%.

In addition, the diffusion through the shell is amplified by swelling even for traces of elements, additives, impurities or other components which might be normally trapped in the implant.

This clearly indicates that additives/components beyond those of medical grades might be released from the implant and yield unexpected tissue reactions. For example the Nusil Med3-6300 is approved with respect to trace elements according the existing guidelines (ASTM E 305).

As the breast implant is subjected to a dynamic load fatigue properties have to be investigated as well. They are known to be decreased by low molar mass media.

Platinum is used as a catalyst in silicone elastomers to start crosslinking. Slightly elevated levels of platinum at the zero oxidation state have been found sometimes for women with implants compared to a control group but no clinical consequences are expected due to the known toxicity of Pt at oxidation state zero (Brook 2006), therefore, leaching of platinum from the breast implant is not an issue. On the other hand potential impurities which cannot be excluded when components are used which do not fulfil medical grade specifications might result in oxidation states of Pt being toxic (Maharaj 2004). Utilizing non medical grade silicone components increase the risk of having traces of heavy metals beyond the Pt *e.g.* tin (Sn), zinc (Zn), chromium (Cr), arsenic (As), lead (Pb), antimony (Sb), nickel (Ni), Copper (Cu). In relation to heavy metals the FDA recommends to analyse these in the "Guidelines for Industry and FDA staff" (FDA 2006). In the same Guideline extractables and releasable chemicals from the implants are recommended to be analysed. It is evident that the extractables and releasable components as described above are strongly depending on the production process and its controlled reliability with respect to a responsible quality management. For the case under consideration (PIP silicone breast implants) these requirements on the process are not fulfilled.

In general, silicone elastomers and gels need to be carefully investigated before approving them for any utilization, in particular a medical one. For example it is known that poly(dimethylsiloxane) (silicone rubber) has poor mechanical properties in the unfilled state, which are improved by the incorporation of mineral filler (Bokobza 2004). The mineral filler (mostly nano and micro scaled) can be an additional effective source for the above described heavy metals, due to their large specific surface.

5.2 Testing procedures on devices

5.2.1 Biological evaluation of medical devices

Toxicological hazards associated risk can be identified by determining the biocompatibility of medical devices or their constituents by applying the EN ISO 10993 series dealing with the biological evaluation of medical devices (ISO, Geneva, Switzerland, CEN, Brussels, Belgium). These standards provide an approach to the biological evaluation of medical devices that combines the review and evaluation of existing data from all sources with, when needed, the selection and application of additional tests, thus enabling a full evaluation to be made of the biological responses to each medical device, relevant to its safety in use. A framework is included for the evaluation and safety testing based on the contact (exposure) time during clinical use.

An important first step in the safety assessment process is a proper and detailed characterisation of the material to be tested. Such characterisation should identify constituent chemicals of the device and possible residual process aids or additives used in its manufacture. This information on the chemical composition of a material may permit identification of potential health hazards before toxicity testing has been initiated This is based on previous testing of the same or very similar materials that has been conducted previously, and/or from information that might be available in the scientific literature. Another important component of the safety assessment process, and establishing whether there exist risks to human health, is a detailed consideration of the patterns of exposure that are likely to occur to various components of the device. In addition to this classical safety evaluation for chemical constituents, a safety evaluation of the final products and/or solid materials relevant to their intended use needs to be performed.

For the identification of any additional testing that may be necessary guidance is provided on the possible assays that may need to be performed for the safety evaluation of a medical device or its constituents. The testing that needs to be considered is based on the use of a medical device (on the surface, as external communicating device, or as

implant), the contact site (mucosal surfaces, blood, or tissues), and the contact time (limited (≤24h), prolonged (>24h but ≤30 days), and permanent (>30 days)) (EN ISO 10993-1: 2009, EN ISO 10993-1:2009/Cor 1:2010). It should be realized that depending on the type of medical device and its application, a range of assays can be selected. For implant devices with prolonged contact the most extensive toxicity testing is indicated including cytotoxicity, sensitization, irritation, acute and subchronic systemic toxicity, genotoxicity, and implantation tests. Additional tests may be indicated by the risk assessment that is performed of a certain medical device/constituent such as biodegradation and toxicokinetic studies, chronic toxicity, carcinogenicity, immunotoxicity, neurotoxicity and reproductive/developmental toxicity. A comparison with a well known existing and accepted medical device/material considered to have an acceptable risk may be used in the safety evaluation of a newly developed medical device/material to determine the relative risk. Ultimately,the final risk assessment incorporating all information available including data obtained by testing needs to be taken into consideration to establish both the potential health risks and the likely benefits that will derive from the use of any particular medical device.

5.2.2 Specific test for breast implants

As noted above (see section3.3) the preclinical evaluation of breast implants includes mechanical tests such as shell integrity (elongation, tear resistance, strength of joints, seams or seals, and design of shell), valve or injection site competence, filling material (compatibility between filling material and shell, test for silicone gel cohesion), implant resistance (static rupture resistance testing, fatigue resistance testing and impact resistance), volume, dimensions, and surface. In addition, chemical evaluation needs to be done including testing of shell material, silicone elastomer or coated materials, filler materials, and a release test on leakage.

5.2.3 Toxicology of silicones

The basic material of silicone breast implants, dimethylsiloxane, is widely used in many industries, various consumer products and medical devices. The various applications may have their specific composition of the silicones, *e.g.* oily products used as lubricants containing low molecular weight oils, and solid elastomers used in various products consisting of highly cross linked polymers. For medical devices medical grade silicones are used which contain a reduced content of low molecular weight polymers. So, in general dimethylsiloxane is considered acceptable safe for human use. Already in 1999 the Institute of Medicine (Washington, USA) conducted an extensive evaluation on the safety of silicone breast implants. In general, the committee concluded in 1999 that the review of the toxicology studies of the silicones known to be used in breast implants does not provide a basis for a health concern at expected exposures. Local complications with silicone breast implants were considered the primary safety issue (Bondurant *et al.*, 1999).

5.3 PIP findings

In 2010 several laboratory studies were performed according to the currently applicable ISO/CEN standards, on retrieved PIP silicone breast implants by the French Health Authorities (AFSSAPS). These tests included testing on silicone chemical composition, shell strength and integrity, and a limited toxicological evaluation.

i) PIP implants

PIP silicone breast implants were made with three different types of shells (smooth, textured, and micro textured) and at least three different types of gels (NUSIL, PIP1, and

PIP2). PIP1 gel was used before 2008, and PIP2 gel was used after 2008. In addition the barrier layer was removed from the shell in 2007. So there are many types of PIP silicone breast implants that have been marketed.

The silicones used in PIP silicone breast implants were not the CE marketed Nusil (MED3-6300) that was indicated as component in the files on PIP silicone breast implants. The Nusil silicones were substituted by other types of (industrial) silicones. The characterization of the raw materials showed that two kinds of silicone gel were used for the filling of PIP prostheses. These raw materials were different from the Nusil gel that was described in the dossier filed by the company. The PIP silicone gels contained significant levels of silicones with low molecular mass. In addition, thermographic analysis showed that the PIP gels were much less stable than the Nusil gel. Regarding the release of silicones considerable variability was observed reflecting a poor reproducibility of the manufacturing process.

Twelve controls (unimplanted implants or preimplants) were mechanically tested—6 textured and 6 smooth implants. The tests for elongation-at-break showed the textured implants were non-compliant, and the smooth implants were compliant. There is no standard for compliance for force-at-break. However, the average force-at-break for textured implants was lower than the average force-at-break for smooth implants. Smooth and textured implants were fatigued tested using the CE Mark technique, and both types were compliant after 2 million cycles. The results of the tensile test and fatigue resistance test comply with the standards (EN ISO 14607). Mechanical tear elongation tests yielded results incompatible with the standard. No cutting, tearing or cracking was observed in PIP silicone breast implants.

The biocompatibility testing was performed according to the EN ISO 10993 series and yielded the following results.

In vitro cytotoxicity testing revealed that the silicone gels used in the PIP silicone breast implants showed no or negligible minimal (<3%) cytotoxicity.

Overall, the genotoxicity of extracts from the gel within the breast implants was investigated in valid genotoxicity tests for the 3 endpoints of genotoxicity: gene mutations, chromosome aberrations and aneuploidy. Samples of the gel were collected from the interior of the implants, after removal of a small part of the shell/membrane of the implant. Extracts of theses samples were obtained by either extraction with 0.9% NaCl or DMSO. The extracts did not induce an increase in the mutant frequency in a gene mutation test in bacteria. A genotoxicity test with mammalian cells was not performed. Exposure of human lymphocytes to the extracts did not result in an increase in cells with chromosome aberrations. The absence of a clastogenic effect was confirmed both in an *in vivo* Comet assay in female mice and in an *in vivo* micronucleus test. In both tests a biologically relevant increase in DNA damage was not observed.
Consequently, based on the present reports the extracts from the gel of PIP breast implants can be considered to have no genotoxic potential. This also indicates that any putative carcinogenic effect of the extracts is due to a non-genotoxic mechanism.

The results of the intra-dermal irritation tests performed showed an irritant potential of the PIP silicone gel that was not found with the silicone gels from other prostheses, nor on the gel declared in the manufacturer's dossier.

ii) Explants

Apparently, no PIP explants have been tested. PIP explants should be tested using the procedure outlined in section 5.7 recommendation for future work.

iii) Additional considerations on PIP implant/explant testing

Any investigation into the effects of implantation time on the durability of implants should separate the implants according to type, so that explants can be compared with the proper controls. This is necessary because the strength of implants can vary considerably according to the manufacturer, the implant type, and the lot-to-lot variability for the given type. For this reason control implant data should be presented with the explant data wherever possible.

There is a lack of testing and analysis on all types of PIP silicone breast implants. Preimplants should be tested and analyzed using the protocol recommended in this report for explants. Mechanical testing should also include patch strength testing and fatigue testing.

Rigorous cyclic fatigue testing should be conducted on preimplants to provide information on the fatigue characteristics of the implants. Fatigue testing should be conducted on the worst case, final, sterilized implants with the thinnest shells allowed by the design release criteria using flat plates that cyclically compress the implants. The implants should be fatigued tested at varying loads or displacements to generate an applied force versus number of cycles to failure (AF/N) curve for each type of implant tested. A minimum of 3 implants from a typical production run should be tested at a given load or displacement. The endurance load (the load at which implants do not fail under cyclic loading) should be established at a minimum of 6.5 million cycles run out. The fatigue data should then be used to predict the fatigue lifetime of the implants

5.4 Conclusions

With regard to the testing of the physical, mechanical and biological or toxicological aspects of silicone breast implants a series of assays is available that can guarantee that the implants used have an acceptable low risk for consumers. Silicones (dimethylsiloxane) in general and thus also the ones used in silicone breast implants contain a certain fraction of low molecular weight polymers that may leach from the implants. These low molecular weight components induce swelling of the elastomeric shell of the implant resulting in weakening the strength of the shell. In addition such silicones may be released from the implant by sweating or leakage after damage or rupture of the implant. In these circumstances also other contents like residual additives or impurities may be released from the implant.

Overall the toxicology studies of medical grade silicones known to be used in breast implants do not provide a basis for a health concern at expected exposures. Local complications with silicone breast implants can be considered the primary safety issue.

The testing of PIP silicone breast implants performed so far shows that the quality of the materials used is not according to the standards for breast implants regarding the elastomeric shell used and the silicone gel filling. A relatively high content of low molecular weight components was present. For the silicone gel filling the genotoxic tests performed showed negative results and cytotoxicty was negligible. The PIP silicone gel was shown to be an irritant in an invivo irritation assay. Especially the latter finding indicates the potential for inducing local tissue reactions when the silicone gel is released from the implant.

6. DATA ON IMPLANT FAILURE RATES AND CONSEQUENCES

Tradition and presumably national trends exist as to which kind of breast implants to use for which kind of procedures. The use of different types of breast implants in European countries is presumably quite similar, although specific brands probably differ among nations. The preference of anatomical implants for reconstructive purposes seems similar, evaluated by presentations at international meetings. In Denmark, the overall majority of implant is textured silicone implants. For reconstructive purposes, most surgeons use anatomical implants with a high cohesiveness gel. For cosmetic augmentation, most use round implants, but some also use anatomical implants. In the US most plastic surgeons prefer smooth implants, the anatomical implant has not been approved for general use yet, and saline filler is still used in about half of the implants.

Based on figures from the Danish Registry for Plastic Surgery of the Breast (Henriksen *et al.*, 2003) and the American Society of Plastic Surgeons (ASPS) (Brody 2009) about 20% of all breast implantations are performed for reconstructive purposes and 80% for cosmetic purposes. A minor proportion concerns congenital malformations.

6.1 User groups and their characteristics

6.1.1 Cosmetic purposes

Women seeking cosmetic breast implantation are generally healthy, normal weight to slim, having given birth, and are on average 32 years old (range, 15-60 years). More women receiving cosmetic breast implants are smokers compared to the back ground population, although national differences are likely (Kjøller *et al.*, 2003, Fryzek *et al.*, 2000, Henriksen and Olsen 2002).

6.1.2 Reconstruction surgery

Women undergoing breast reconstruction are either former breast cancer patients (in case of secondary reconstruction) or patients undergoing reconstruction at the time of their mastectomy (primary breast reconstruction). This group includes women with invasive breast cancer and women with in situ cancer in addition to women with a familial disposition to breast cancer, who undergo prophylactic mastectomy and reconstruction.

Breast cancer patient are generally fairly healthy patients besides their cancer. Most patients are free of their illness at time of reconstruction, or in case of primary reconstruction the disease is considered local, or perhaps local-regional. Most breast cancer patients receive adjuvant chemotherapy or endocrine therapy and some also radiation therapy. The average age at time of reconstruction in a Danish registry based material, was 50 years, with a range of 21-72 years (Henriksen and Olsen 2002)

In (former) breast cancer patients undergoing reconstruction the soft tissue layer over the implant is much thinner than in augmented women. The tissue is often quite tight, and in case of previous radiation therapy the tissue is always more fibrotic and un-elastic than if radiation therapy was not used.

It is well known that complications after implantations are much higher in the breast reconstruction cohort than among augmented patients (Henriksen *et al.*, 2005, Cunningham and McCue 2009, Spear *et al.*, 2007). This is multi factorial, for instance due to the operation technique, the amount of tissue available, the laxity of the tissue, the concomitant surgical trauma of mastectomy in primary cases, former tissue damage in case of chemotherapy and radiotherapy in secondary cases.

No studies have compared women with breast augmentation with women with reconstructed breasts with regard to vulnerability. Several good explanations for the

different profile of complications exist, but some may in fact be due to different vulnerability in general and perhaps also due to tissue specific factors.

No scientific studies are available to indicate if for instance former breast cancer patients would be more likely to get symptoms from a PIP implant rupture than cosmetic breast augmented patients.

6.2 Methods for identifying failure of breast implants

6.2.1 Clinical diagnosis

Clinical breast examinations have little sensitivity for detecting implant rupture; only positive signs provide useful information, but lack of findings does not rule out implant rupture. In order to exclude implant rupture in the absence of positive signs, more sophisticated diagnostic tools such as MRI are needed, in line with the findings of other studies (De Angelis *et al.*, 1994, Middleton 1998, Hölmich *et al.*, 2005).

Positive signs of implant rupture that sometimes can be detected at physical examination are softened breast consistency or palpable nodules or masses adjacent to the implant (Cohen *et al.*, 1997, Hölmich *et al.*, 2005). Enlarged lymph nodes in the nearest axilla does not necessarily correlate to implant rupture, as enlarged nodes can be found in association with intact implants due to short chain silicone gel migration (sweating). However, taking the patients history into account can add valuable information: a sudden swollen lymph node which also may be sore can be the sign of a new rupture (Ahn and Shaw 1994, Brown *et al.*, 1997, Shaaban *et al.*, 2003).

6.2.2 Magnetic resonance imaging

There is international agreement that Magnetic Resonance Imaging (MRI) is by far the most accurate modality for diagnosing breast implant rupture. In scientific validation studies it has been found to detect silicone breast implant rupture with very high accuracy; with an up to 99% positive predictive value as compared with diagnosis at surgery (Hölmich *et al.*, 2005). Implant rupture is characterized by the linguine sign showing that the breast implant contains multiple curvilinear low-signal-intensity lines within the high-signal-intensity silicone gel (Safvi 2000). The lines are usually scattered diffusely and appear as long strands of decreased signal intensity curved on top of each other. In other studies, comparable or a slightly lower accuracy was found (DeAngelis *et al.*, 1994, Everson *et al.*, 1994, Ahn *et al.*, 1994, Berg *et al.*, 1995, Morgan *et al.*, 1996, Quinn *et al.*, 1996, Soo *et al.*, 1997, Middleton, 1998, Ikeda *et al.*, 2000). A meta-analysis estimated the summary sensitivity to 78% (95% CI, 71–83) and the summary specificity was 91% (95% CI, 86–94) (Cher *et al.*, 2001).

Performance of MRI in a screening setting with much lower prevalence of implant rupture than in the above validation studies is bound to be less precise, but this has not been studied in a prospective setting (McCarthy *et al.*, 2008). In general, the higher sensitivity a method is aiming for, the lower becomes the specificity, and false positives as well as false negatives increase in a setting with few ruptures (McCarthy *et al.*, 2008, Song *et al.*, 2011).

6.2.3 Ultrasonography

Ultrasonography is the second best imaging modality for detecting implant rupture, but it is less precise and more operator dependent (Ahn *et al.*, 1994, Gorczyca *et al.*, 1998, Ikeda *et al.*, 2000). But since the price of an ultrasonography is much lower than MRI it is probably used much more often, and has in clinical algorithms been used as first choice examination (Song *et al.*, 2011, Chung *et al.*, 1998).

6.2.4 Conclusions

When using MRI or ultrasonography, the criteria used to diagnose rupture are very important. Consensus exists (based on validation studies) that certain signs are diagnostic (linguine sign, subcapsular lines etc.). In some cases, specific signs may give suspicion of rupture. However, a conclusive diagnosis cannot be made. Therefore most studies classify results as **certain ruptures, possible ruptures and intacts**, and this is also applicable in a clinical setting. Mammography is not useful to evaluate the implant; structures within the implant cannot be seen. Extracapsular silicone can be seen on a mammogram.

It should be noted that the only country with specific recommendations for diagnosis of implant ruptures is the US: here a baseline MRI is advised 3 years after implantation and then every 2 years.

6.3 Failure of breast implants in women

6.3.1 Terminology

Differences in diagnostic criteria and implant time in situ likely account for the large discrepancies in the reported number of ruptures in different clinical studies. A certain terminological confusion exists in the literature, making direct comparisons of studies difficult. A frank rupture with a visible defect in the silicone membrane is unequivocal; however, smaller defects, known as 'pinhole defects', can be missed unless the implant is examined carefully. Gel-bleed or gel-sweat is the diffusion of short-chain silicone oils over an intact silicone membrane, so that an oily, slippery surface is a normal finding during explantation of intact first- and second-generation implants (Dowden 1993). Third-generation implants have a so-called 'low-bleed membrane', designed to diminish such diffusion. Sticky silicone with thread-like formations on the outside of the membrane can be mistaken for gel-bleed but in fact indicates a rupture, as the long-chain silicone molecules which are responsible for the thread- like formations cannot diffuse through an intact membrane (Peters *et al.*, 1994, Peters *et al.*, 1999, Dowden 1999, Hölmich *et al.*, 2005). Some authors have grouped implants with gel-bleed with ruptured implants, and some have presumably not differentiated between gel-bleed and tiny ruptures (Robinson *et al.*, 1995, Beekman *et al.*, 1997).

Ruptured or failed implants should only include implants with ruptures – not gel-bleed or sweating. Whether a ruptured implants shell has large or small holes can be of academic interest, but is not necessarily clinically relevant, although the amount of free silicone affects the effort required to remove it from the implant pocket.

Ruptures can be **intracapsular**, meaning that the free silicone gel is present outside the implant but kept within the intact fibrous capsule which forms around the implant. Intracapsular rupture can go unrecognized as there may be no accompanying change in the configuration of the breast, no patient complaints, and no physical diagnostic finding. In an **extracapsular rupture**, free silicone is found on the outside of the fibrous capsule, typically adjacent to the capsule as nodules or lumps. Such lumps contain free silicone surrounded by inflammatory cells, especially macrophages. The terms intra- and extracapsular rupture is mainly used in imaging, whereas clinical evaluation can be less clear.

A **silent implant rupture** is a rupture which was not suspected clinically or from the patients symptoms, but discovered at imaging or surgery. Such ruptures are not noticed because the leaking silicone is kept in place by the surrounding fibrous scar membrane (the fibrous capsule), which has adapted its shape from the implant and no visible re-absorption occurs.

The number of ruptured implants in a specific group of women is denoted the proportion of ruptures. The rupture rate is expressed in time and this indicates that observation period is involved; i.e.; number of ruptures per capita per year or number of ruptures per 100.000 women-years etc – comparable to other incidences. In most literature about ruptures, rupture rate is used instead of rupture proportion, and the quantity is expressed as a percentage. This is not correct, but common.

6.3.2 Time to rupture

It is well established that the rupture of breast implants tends to increase with the time since implantation. There is some indication that PIP devices have an increased likelihood to rupture at earlier times than breast implants from some other manufacturers. This observation needs confirmation.

6.3.3 Causes of failure

Breast implants can fail for a variety of reasons including: (1) inadvertent instrument damage during surgery, (2) open capsulotomy, (3) closed capsulotomy, (4) needle biopsy or hematoma aspiration, (5) shell wrinkling, (6) trauma, (7) mammography, (8) implantation surgery, (9) explantation surgery, (10) manufacturing defects, (11) cyclic fatigue, and (12) patch detachment.

Wear patterns that create pinhole defects have been identified around creases and folds, and areas of folded membrane have been shown to be significantly weaker than adjacent unfolded membrane (Brandon *et al.*, 2001, 2006, Richardson *et al.*, 2002).

Implant ruptures can take many forms, from a small pinhole defect to larger tears in the membrane. Defects are sometimes found in an area where the posterior patch is 'welded' to the remaining implant. Old implants can present with an almost disintegrated membrane. In 1988, Van Rappard and co-workers used a simple test to show that the breaking pressure of explants was negatively correlated with time after implantation. They also found that the pressure used for closed capsulotomy tended to exceed the breaking pressure in older implants, sufficient to cause implant rupture (Van Rappard *et al.*, 1988).

Studies on the mechanical properties of implants have shown mixed results, some indicating a decrease in membrane strength with increasing implantation time (Phillips *et al.*, 1996, Greenwald *et al.*, 1996) but with significant variation by brand, type and even within lots (Phillips *et al.*, 1996, Greenwald *et al.*, 1996, Brandon *et al.*, 2001b, Marotta *et al.*, 2002). A consistent finding is swelling of the membrane, due to uptake of silicone oils or serum lipids, which reduces shell strength (Marotta *et al.*, 2002, Adams *et al.*, 1998, Brandon *et al.*, 2003, Birkefield *et al.*, 2004). After a time, equilibrium sets in and no further swelling or decrease in strength is found, at least in Dow Corning implants (Brandon *et al.*, 2003). After the oils have been extracted, however, the original strength of the membrane is more or less regained in comparison with controls from the same lot that have never been implanted, indicating that the membrane is not 'dissolved' by such swelling (Brandon *et al.*, 2002, Lane and Curtis 2005, Taylor *et al.*, 2007). Some authors have other results (Marotta *et al.*, 2002) and, from a clinical point of view, it is difficult to understand why some membranes do not deteriorate over time, while in other cases very fragile, gelatine-like membranes must be picked out piece by piece during explantation. However, this can be explained by considering shell strength characteristics. Breast implants fail due to the mechanisms that generate damage to the shell. Daily activity body motion, such as walking and running, induces forces on implants. These *in vivo* forces are cyclic and repetitive. Over time the cumulative *in vivo* cyclic loading induces damage to the implant which can result in failure. The rate of damage accumulation can be accelerated for implants with thin or structurally weak shells at the time of implantation. Increased shell swelling can also accelerate the rate of damage accumulation that subsequently could result in shell failure.

6.3.4 Silicone implant survival and rupture

6.3.4.1 Implant survival

Attempts have been made to estimate implant survival by pooling data on explantations (Robinson *et al.*, 1995, Beekman *et al.*, 1997, Goldberg *et al.*, 1997, Marotta *et al.*, 1999). As described in detail below, the use of prevalence data to estimate rupture incidence is problematic. It is at best a surrogate for incidence, and selection bias is a significant risk in such studies. On the basis of their 'master failure curve' based on data from 35 studies with more than 8000 explants, Marotta *et al.* (1999) conducted a retrospective failure analysis for explanted silicone gel-filled breast implants (8000 explants from 35 studies) and found a statistically significant correlation between implant duration and elastomer shell failure (25% within 3.9 years and 71.6% at 18.9 years). An update of that analysis (9774 explanted implants from 42 studies) revealed 26% failure at 3.9 years, 47% at 10.3 years, and 69% at 17.8 years (Marotta *et al.*, 2002). These percentages were arrived at by studying only women who elected to undergo explantation. Because women with severe enough complaints to undergo explantation likely have much higher rupture rates than asymptomatic women, the reported rupture prevalence rates overestimate the rupture prevalence for all women with implants, as asymptomatic women are usually not part of the studies. Marotta *et al.* found a general reduction in tensile strength, tear strength and elongation of explanted silicone elastomer shells and concluded that their explant rupture data are representative of the implant aging properties and rupture characteristics of the general population of silicone gel-filled breast implants that remain implanted. The fact that prevalence of rupture increases over time is not surprising since prevalence is a cumulative measure at a given moment in time. This, however, does not mean that the *probability* of rupture during a specified time period (incidence) increases with increasing implant age, a conclusion that cannot be drawn from the highly selected cross-sectional data analyzed by Marotta *et al.* (2002). This study has also been criticised for biased reporting of the literature(Young *et al.*, 1998, Cook *et al.*, 1999,2002).

Goodman *et al.* reported a meta-analysis of data on explants but used a stricter method, including only the results of five explantation studies (Goodman *et al.*, 1998). Separate Kaplan-Meier survival curves were presented for each study, some of which were within range of that shown in Figure 2 (see below). The study was criticised for not including information about implant generation, as there are large differences in design and durability (Peters *et al.*, 1999). Peters, in a response to this study, showed the survival curves for second-generation implants at his centre; clear differences were seen by manufacturer, Surgitek implants being significantly less durable than Heyer-Schulte and Dow Corning implants, in line with findings in the Danish prevalence study (Peters *et al.*, 1999, Hölmich *et al.*, 2001).

6.3.4.2 Implant rupture

Estimates of breast implant rupture prevalence range widely, in part because the methods of estimating rupture prevalence rates differ among studies (Bondurant *et al.*, 1999; Brown *et al.*, 2000; Handel *et al.*, 2006; Heden *et al.*, 2006a, 2006b; Marotta *et al.*, 1999, 2002; Robinson *et al.*, 1995; Slavin and Goldwyn, 1995). Determination of the frequency of gel migration outside the fibrous capsule is more difficult than ascertainment of rupture prevalence, unless there is implant retrieval (which is usually done in symptomatic women) and examination of explant and tissue.

An MRI study of almost 300 women (533 cosmetic breast implants) randomly picked from a larger study base underwent MRI in 1999, with a median implantation time of 12 years at MRI (Hölmich *et al.*, 2001). This study established the baseline prevalence of implant rupture among a random sample of women with silicone breast implants. A large number of implants were found to be ruptured (26% of implants, and found in 36% of

women. An additional 6% of implants were given the diagnosis of possible rupture). Of the ruptures, 31 (22%) were extracapsular, affecting 23 women (8%) in the study group. Extracapsular rupture was significantly associated with a prior closed capsulotomy. Rupture prevalence was correlated with implant generation, time in situ and also brand (Dow Corning, McGhan, Eurosilicone, Surgitek, and about 100 unknown implants were examined).

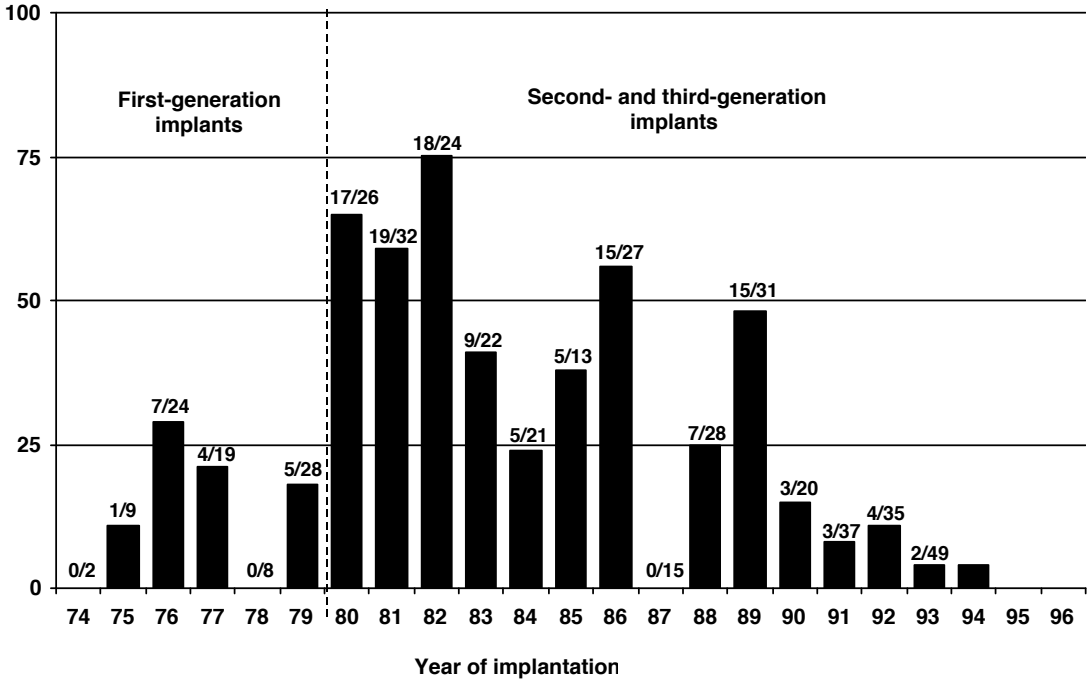

Figure 1: The proportion of ruptured implants at the baseline MRI examination by year of implantation. Figures on top of bars indicate that for instance 18 of 24 implants examined from that particular year were ruptured at MRI (Hölmich *et al.*, 2001).

In a US FDA-funded study published shortly before the Danish prevalence study, Brown *et al.* also examined the prevalence of rupture diagnosed by MRI among a selected group of 344 women with silicone breast implants from two plastic surgery clinics (Brown *et al.*, 2000). The authors found that 69% of the women had a definitely ruptured implant, compared to the Danish 36%. The median implant age at rupture was estimated to be 10.8 years. Extracapsular migration of gel was seen in 85 (12.4%) breasts in 73 (21.2%) of the women. This discrepancy between these and the Danish results is probably due to differences in the types of implants examined: Brown *et al.* examined mostly second-generation implants and a much higher proportion of Surgitek implants (70% vs. 15% in the Danish study). The latter were found to have the highest prevalence of rupture of all the brands studied (Brown *et al.*, 2000).

Handel *et al.* (2006) conducted a study of 1529 consecutive women who received 3494 implants (1137 saline-filled, 778 double lumen, 1537 silicone gel- filled, 38 other) for augmentation, reconstruction or revision at a clinical practice between 1979 and 2004. Rupture diagnosis was based on clinical confirmation at the time of explantation and not on the basis of mammography, ultrasound or MRI findings. After a mean follow-up of 37.4 months (range, 0-23.3 years), silicone implant ruptures occurred in 14 of 1,123 smooth implants, six of 618 textured implants, and eight of 568 polyurethane foam-covered implants, yielding crude prevalence rates of 1.2%, 1.0% and 1.4%, respectively.

MRI rupture screening of 144 Swedish women with 286 fourth generation cohesive silicone breast implants yielded a rupture prevalence of 0.3-1.0% at an average of 6

years post-implantation (Heden *et al.*, 2006a). In a recent multi-center European study, MRI examination of rupture in women with 199 third generation silicone gel-filled breast implants with a median implantation time of almost 11 years revealed a rupture prevalence rate of 8% (Heden *et al.*, 2006b).

It is difficult to compare the results of cross-sectional rupture prevalence studies, for several reasons. Studies often include women with different generations of implants (often not the third or fourth generation single-lumen silicone gel-filled implants currently in use), saline and silicone implants, and implants made by different manufacturers. Studies of rupture prevalence are also likely biased in favor of higher rupture prevalence, since many publications present rupture data for implants that had already been explanted because rupture was suspected. Moreover, studies present data on women with different follow-up periods, and determination of rupture has been based on different detection methods (*e.g.*, explantation, ultrasound, mammography, MRI, clinical survey results in patient cohorts), all with varying sensitivity and specificity. As a result, findings cannot be generalized to the universe of all women with breast implants.

Implant age has been commonly noted in the literature as a determinant of rupture, with risk of implant rupture increasing with implant age (De Camara *et al.*, 1993; Feng and Amini, 1999; Holmich *et al.*, 2003; Rohrich *et al.*, 1998). Holmich *et al.* (2001) found that age of implant was significantly associated with rupture prevalence among second and third generation implants. However, despite the small number of first generation implants, the prevalence of rupture among first-generation implants, which had thick shells and highly viscous gel, was substantially lower than thin-shelled second-generation implants, despite the longer implantation time.

The Institute of Medicine, in 1999, concluded that quantitative data on rupture incidence over time were lacking for all breast implant types, including third generation implants (Bondurant *et al.*, 1999). Only one study, the Danish MRI study of rupture prevalence by Holmich et al, has employed a valid study design to also detect true rupture incidence (Holmich *et al.*, 2003). Two years after the baseline MRI, the same population of women were examined again with MRI. A true rupture incidence analysis was performed based on 317 implants (in 186 women) that were intact at the baseline MRI (n=280) or were intact at baseline but removed before the second MRI (n=37) (Holmich *et al.*, 2003). The authors observed an overall rupture incidence rate for definite ruptures of 5.2% per year. The rupture rate increased significantly with implant age. For third generation implants (barrier-coated, low bleed implants available since 1988), the rupture-free survival was estimated as 98% at 5 years and 83%-85% at 10 years. Based on these figures, a survival curve was created (Figure 2).

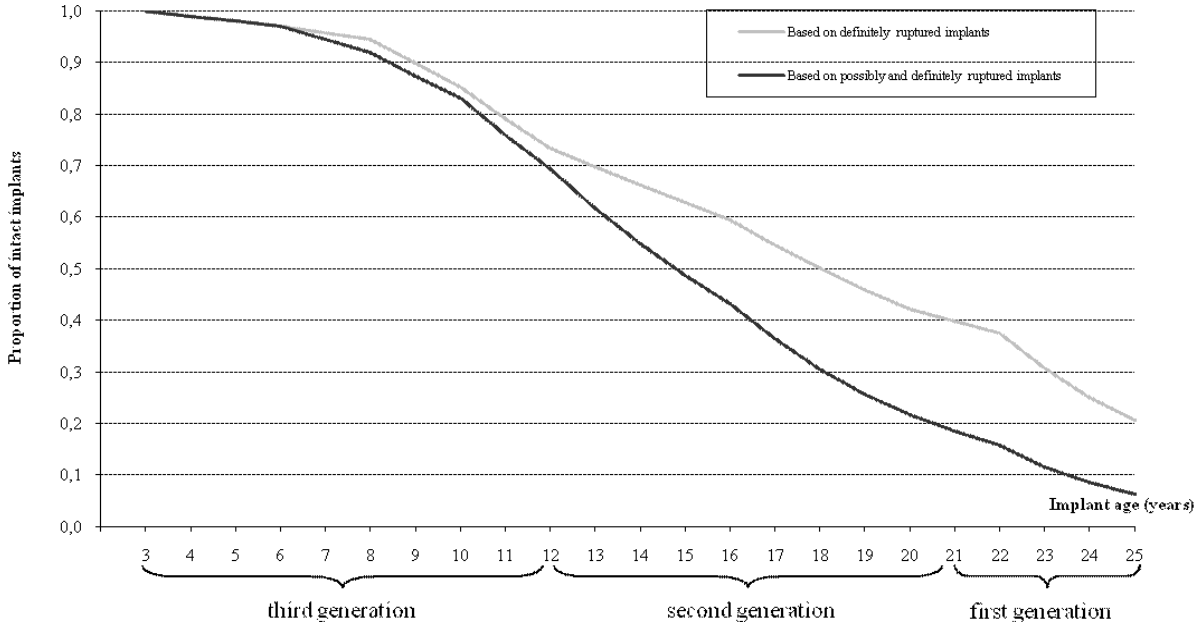

Figure 2: Estimated rupture-free survival curves based on definite ruptures or on definite and possible ruptures combined for all implants implanted at least 3 years before the baseline MRI (Hölmich *et al.*, 2003).

The results of the prevalence and the incidence study concur relatively well. In the prevalence study, 3% of 3–5-year-old third-generation implants and 16% of 6–10-year-old implants were ruptured, while in the incidence study, it was estimated that approximately 2% of third-generation implants would be ruptured by 5 years and 15–17% by 10 years. The third-generation implants were relatively durable for the first 6–8 years, after which the rupture rate increased. The results of previous explantation studies are in line with these studies, indicating that first- and third-generation implants are the most durable, whereas second-generation implants are associated with a much higher frequency of rupture (De Camara *et al.*, 1993, Malata *et al.*, 1994, Robinson *et al.*, 1995, Peters *et al.*, 1997, Cohen *et al.*, 1997, Rohrich *et al.*, 1998, Feng and Sharpe 1999, Collins *et al.*, 2000).

The overall estimate of implant rupture prevalence in the first Danish study (Hölmich *et al.*, 2001) is somewhat lower than those reported in clinical explantation studies (De Camara *et al.*, 1993, Malata *et al.*, 1994, Robinson *et al.*, 1995, Peters *et al.*, 1997, Cohen *et al.*, 1997, Rohrich *et al.*, 1998, Feng and Sharpe 1999, Collins *et al.*, 2000). Those studies were, however, based mainly on symptomatic women who elected for surgery, who are likely to have a higher proportion of ruptured implants than unselected women. Moreover, damage to implants during explantation can also lead to an overestimation of *in vivo* failure prevalence (Slavin and Goldwyn, 1995).

6.3.4.3 Third-generation implants

Two reports on implant durability in third-generation implants became public as a result of applications by two implant manufacturers for pre-market approval by the US FDA in 2005 (Heden *et al.* 2006, Collis *et al.* 2007). In a multinational study on Inamed (now Allergan) implants, 8% of 199 implants (both smooth and textured) in 15% of the 106 participating women were diagnosed as ruptured or possibly ruptured at MRI, after a median implantation time of 10.9 years (range, 9.5–13.2 years) (Heden *et al.* 2006). These implants would be categorised as third generation implants. A British study of 149 women with Mentor Siletex gel implants for subglandular breast augmentation was published in 2007 (Collis *et al.* 2007). The same data were included in Mentors pre-

market approval (FDA 2006). Eleven percent of implants in 15% of women were diagnosed with rupture at MRI after a mean implantation time of 8.8 years (range, 4.8-13.5 years). At subsequent surgery on a subset of the study population, 29% were false-positives and 4.9% were false-negatives, the rest of implants correctly diagnosed at MRI. The positive predictive value was 61% and the negative predictive value 82%. Using both radiological and explant data, a survival estimate was calculated, showing that by 13 years of implantation, 19% and 12% of Mentor Siltex implants, respectively, will be ruptured. Actually, these figures were seen after 10 years of implantation, but became more precise with larger follow-up. The data from the Allergan and Mentor studies are comparable to the finding in the Danish study, that 7–14% of third-generation implants, with a median age of 6–7 years, were ruptured, depending on the definition of generation (Hölmich *et al.* 2001). The manufacturer-specific rupture prevalences are, however, somewhat better than those in the survival curve from the Danish Rupture incidence study (Hölmich *et al.* 2003) with 17% ruptured implants by 10 years, which is based on several brands of implants.

In the recently published data from 8 and 10 year follow-up on the Core Study patients from Allergan and Mentor breast implants higher cumulative ruptures have been reported. For the Allergan implants, 10-year cumulative MRI diagnosed ruptures were ranging from 6.7 % (95% CI, 2.8-13.7) to 27.2 % (95% CI 17.3-41.3) depending on study group (revision augmentation and primary reconstruction, respectively). For the Mentor implants, 8-year cumulative MRI diagnosed ruptures ranged from 13.6% (95% CI 7.6-23.6) in primary augmentation patients to 21.3% (95% CI 7.3-53.3) in the revision reconstruction group. It is unclear how many of these ruptures have been verified in surgery (FDA 2011).

6.3.4.4 Fourth-generation implants

A few case reports and one large study of the integrity of fourth-generation implants have been published (Shaaban *et al.* 2003, Lahiri and Waters 2006, Heden *et al.* 2006). The case reports demonstrate the ability of cohesive implants to generate extracapsular silicone and enlarged lymph nodes (Shaaban *et al.* 2003, Lahiri and Waters 2006). Heden *et al.* studied 144 women with 286 McGhan/Inamed style 410 implants (maximal cohesive gel), with a median implantation time of 6 years (range, 5–9 years). At MRI examination, one implant (0.3%) was ruptured and two implants (0.7%) had intermediate signs of rupture (Heden *et al.* 2006). Heden *et al.* did a similar study, which was published in 2009, with MRI on 163 women with Allergan style 410 implants; 1.7% were diagnosed as ruptured at MRI after a median implantation time of 8 years (Heden *et al.* 2009). These results indicate that cohesive implants are more durable than the previous generations; however, the silicone membrane of these cohesive implants is identical to that in the third-generation implants of the same manufacturer examined in the study cited above, (Heden *et al.* 2006), and the accuracy of MRI diagnoses of rupture in these implants has not been studied.

6.4 Health effects of silicone breast implants (SBI)

6.4.1 Local effects in the breast

Based on clinical experience, some women with breast implants present discrete symptoms, suspected of being due to implant rupture. The typical history is a change in the breast configuration, often towards a softer breast, but sometimes as increased hardness. Both can be indicative of a rupture, as described above. In some cases, a swollen and sore lymph node in the lateral breast or the adjacent axilla is the first clinical sign of an implant rupture. The changes have typically taken place over a few months, but in case of swollen lymph nodes most women seek medical evaluation soon after onset of symptoms (Dowden 1993, Hölmich *et al.*, 2005). Some women have pain in the

breast, rarely described as serious, but more like an inner soreness or itching (Hölmich *et al.*, 2005). These symptoms, along with a clinical examination can often give the suspicion of rupture, however, ultrasonography or preferably MRI must be performed in order to verify the diagnosis. In many cases, there may be additional indications for surgery and the imaging part can be left out. In case of an unequivocal clinical examination, a rupture may still be present, and imaging is necessary.

A few studies reported higher frequencies of complaints by women with breast implants ruptures. However, no specific pattern of symptoms was identified (Wells *et al.*, 1994, Hennekens *et al.*, 1996, Englert *et al.*, 2001, Fryzek *et al.*, 2001). A large number of women must have had silent implant rupture at the time of study, based on knowledge from rupture studies.

In order to evaluate breast symptoms as well as more general symptoms in case of untreated implant rupture, a Danish study examined 64 women with 96 implant ruptures which were left untreated over a two-year period (Hölmich *et al.*, 2004). The ruptures were diagnosed at an MRI in 1999, the patients did not have symptoms that warranted explantation at the time of diagnosis and choose to take a "watchful waiting approach". After two years, a new MRI was performed. 11 implants (11%) in 10 women with had progression from intra- into extracapsular rupture (n = 7), as progression of extracapsular silicone (n = 3) or as increasing herniation of the silicone within the fibrous capsule (n = 1). In most cases, these changes were minor. Some of the changes could be ascribed to trauma, but others appeared to be spontaneous. The presence of autoantibodies (Rheumafactor, ANA, Cardiolipin) decreased slightly over time in all women and did not appear to be influenced by implant status. None of the nine women with new or increased extracapsular silicone at the second MRI became seropositive for any of the measured autoantibodies (Hölmich *et al.*, 2004). Women with untreated implant ruptures reported a significant increase in non-specific breast changes (OR, 2.1; 95% CI, 1.2–3.8) when compared with women without ruptures. The changes were primarily a softer breast with a different shape and size and in some cases pain, although not considered serious. The commonest remark was that the breast felt flatter and smaller. Although based on small numbers, there was no excess reporting of new diseases among women with ruptured implants (OR, 0.7; 95% CI, 0.3–1.6). This is the only study to examine untreated ruptures.

Women with extracapsular ruptured implants more frequently reported breast hardness indicative of capsular contracture than women with intact implants. This is consistent with the ability of free silicone to induce a foreign body reaction that can result in fibrosis (Caffee 1986). The fibrous capsule surrounding the implant has been found to act as a natural boundary for silicone, with high levels observed in biopsy samples of capsules and considerably lower concentrations in the breast parenchyma, regardless of implant status (McConnell *et al.* 1997, Peters *et al.* 1996, Schnur *et al.* 1996, Beekman *et al.* 1997). In the study by Beckman *et al.*, there was significantly less silicone migration over the fibrous membrane in women in whom the capsule was calcified and significantly more in patients in whom implantation exceeded 12 years. There was no significant correlation between the status of the implant (intact, bleeding or ruptured) and the degree of silicone migration (Beekman *et al.* 1997). Mechanical stress and trauma, such as manual capsulotomy, have been associated with extracapsular silicone gel leak (Ahn and Shaw 1994, Eisenberg *et al.* 1977, Hölmich *et al.* 2001), but the mechanism of spontaneous migration has not been fully clarified. In the above mentioned Danish study of untreated ruptures intracapsular rupture spontaneously became extracapsular in a few cases (Hölmich *et al.* 2004). This lends further support to the understanding that intracapsular or extracapsular implant rupture is not a permanent condition and that the fibrous capsule, although solid and sometimes even calcified, is not impermeable to silicone, as seen in both pathological specimens and on MRI.

Some studies have found no association between capsular contracture and implant rupture,(Peters *et al.*, 1994, Collins and Sharpe, 2000) whereas a study of 1619 removed implants found a significant association (OR, 1.52; 95% CI, 1.14–2.03) (Feng and Amini

1999) similar to that in a smaller Danish study (Hölmich *et al.* 2005). All of the reported studies, however, involved symptomatic patients who had undergone explantation, and this might have biased their results. There may be an association between significant capsular contracture and implant rupture, but mutual confounding of both events with increasing implant age makes it difficult to evaluate the true effect. In any case, the association does not appear to be strong.

Women with silicone gel-filled breast implants sometimes develop local and peri-operative complications including serious infections, severe or chronic breast pain, hematoma and the need for additional surgery. Many of these post-operative complications are not unique to breast implantation but occur following various types of surgery in general. Prospective data on the occurrence of local complications following breast augmentation have accumulated in the literature, with several recent reports reporting on the newer generations of implants, although long-term data still remain somewhat limited for these newer highly cohesive implants. There are no epidemiologic data available specifically addressing local complications among recipients of PIP silicone breast implants, however, a review of what is known regarding local complications and cosmetic breast implants in general will provide information and context to this issue.

The reported frequency of local complications among silicone breast implant recipients generally ranges between 17% and 36% (Spear *et al.*, 2007; Cunningham 2007; Hvilsom *et al.*, 2009; Kjoller *et al.*, 2002b; Henriksen *et al.*, 2003, 2005; Fryzek *et al.*, 2001; Kulmala *et al.*, 2004). This variability among studies reflects differences in patients' physical conditions and co-morbidities, implant design, and timing of occurrence of complications. Studies including newer generations of implants and textured implants generally report lower complication frequencies compared with studies of earlier generations of implants. Typically, the most frequent local complication is capsular contracture, with frequencies ranging from 1.9 to 23% in recent reports, while complications such as pain, hematoma, and wound infection are substantially less common and occur during the acute postoperative period, with frequencies generally less than 2%. Additional surgery after primary implantation has been reported as a result of complications in 10 to 30% of implantations. Capsular contracture is the most frequent reason for additional surgery in women with breast implants.

Reports of complications following implantation with the newer generations of implants were published recently by two large implant manufacturers. Spear *et al.* (2007) reported results for 455 women (with 908 Inamed/Allergan implants). During six years of follow-up, the most common local complication was severe capsular contracture (Baker III/IV) which occurred in 15% of the women and was the primary indication for approximately 30% of reoperations. The frequency of capsular contracture is higher in this study compared with others and may be attributed to the fact that only 41% of the implants were textured implants, which have been reported to have a lower incidence of capsular contracture (Collis *et al.* 2000; Wong *et al.*, 2006). Other complications reported after primary augmentation were implant malposition and asymmetry occurring in 5.2% and 3.0% of the women, respectively. Breast pain and swelling occurred among 9.6% and 8.3% of women, respectively, but most often as postoperative complications that resolved within two months after surgery. Twenty-eight percent of the women underwent a reoperation within six years, seven of whom had more than one reoperation.

Cunningham *et al.* (2007) reported results for 551 patients with Mentor implants and three years of follow-up. Severe capsular contracture (Baker III/IV) was the most common complication observed in 8.1% of the women. Fifteen percent of the women underwent a reoperation within three years, of which 36.7% were due to capsular contracture, 11% to hematoma and 4.6% to asymmetry.

In a multi-site European study of Allergan Style 410 highly cohesive, textured implants (Heden *et al.* 2009), with longer follow-up of 5 to 11 years after implantation, capsular contracture was detected by for 5.3% of implants, consistent with a rate of 5.6% reported in an earlier study by Heden *et al.* (2006) of the same implants. All were grade III capsular contractures. A three-year follow-up study in the United States of 492

women with cosmetic augmentation using the same Style 410 highly cohesive implants (Bengtson *et al.* 2007) reported low complication rates; implant malposition was most common (2.6%), while grade III/IV capsular contracture occurred among 1.9% and other complications, including breast pain, infection or swelling, among less than 2% of women. The risk of reoperation among augmented women was 12.5%, and the primary reasons for reoperation were implant malposition or patient request for size/style change; capsular contracture was the primary reason for reoperation among 6.9% of women in this study.

Cohort studies conducted in Denmark (Hvilsom *et al.*, 2009; Kjoller *et al.*, 2002b; Henriksen *et al.*,2003, 2005), Sweden (Fryzek *et al.*,2001) and Finland (Kulmala *et al.*,2004) have investigated local complications among women with cosmetic breast implants. Hvilsom *et al.* (2010) reported the most recent, long-term prospectively acquired data on local complications from the population-based, prospective Danish Registry for Plastic Surgery of the Breast. The incidence and severity of short-term complications was examined in 5373 women (10 640 implants) who underwent primary cosmetic breast implantation between 1999 and 2007, with a mean follow-up of 3.8 years (range up to 8.7 years); 35% of women had at least 5 years of follow-up. Overall, 97% of the implants were silicone gel filled and 93% had a textured surface. Of the silicone gel-filled, textured implants, 65% were older, less cohesive gel implants, 14% were newer, more cohesive gel implants, and 21% were the newest, very cohesive gel implants. The frequencies of complications among women in this study were generally lower than those reported in other studies, likely due to some underestimation of complications attributable to passive surveillance used by the Registry, as opposed to proactive regular and frequent examinations according to protocol performed in a clinical study. During the entire follow-up period, 16.7% of women developed at least one adverse effect and 4.8% developed a surgery-requiring complication. Within 30 days of implantation, the most common adverse events were infection (1.2%) and hematoma (1.1%), while change of tactile sense (8.7%), asymmetry/displacement of the implant (5.2%) and mild capsular contracture (4.2%) were most common within five years. Less than 1.5% of women reported prolonged pain in the breast within three years or five years following implantation. The frequency of severe capsular contracture (Baker Grade III-IV) was 1.3% within three years and 1.7% within five years after implantation. Displacement or asymmetry (39.9%) and capsular contracture (17.3%) were the most frequent clinical indications for reoperation.

An earlier report from the Danish Implant Registry, based on shorter follow-up, examined determinants of surgery-requiring complications and capsular contracture among 2,277 women who underwent cosmetic breast implantation from 1999 through 2003 (Henriksen *et al.*, 2005). Most implants (76%) contained soft silicone gel (third-generation implants) while 22% contained firm, cohesive gel (fourth-generation implants). During an average follow-up of 119.5 months (range 3-50 months), 12% of implants (17% of women) had short-term complications, of which 136 (3.0%), corresponding to 4.3% of women, required surgical intervention. Capsular contracture grades III through IV was registered among 30 women, 9 of them bilaterally. The most frequent clinical indications for surgical intervention were asymmetry/malposition of implant (38% of surgeries) and capsular contracture grades III to IV (16%). Other less common implant-related complications requiring surgery included periprosthetic infection (1.5%) and breast pain (3.7%). Unsatisfactory cosmetic result was an indication for 51% of the 136 revision procedures.

In their recent clinical practice-based study, Handel *et al.* (2006) reported that the rate of capsular contracture grade III or IV was 1.99 per 1000 patient-months after augmentation and 4.36 per 1000 patient-months after implant revision surgery. The frequency of hematoma and infection ranged between 1.5% and 2.1% following augmentation or revision surgery. For breast augmentation, 248 of 1,601 (15.5%) implants required subsequent reoperation, while 21.9% of implants used for revision surgery required subsequent reoperation. The most common reason for reoperation was capsular contracture (56% of patients requiring additional surgery).

There have been additional recent reports on the occurrence of specific local complications following breast implantation. Fryzek *et al.* (2001) analyzed local complications, based on medical record review, among 1,280 Swedish women with cosmetic breast implants, and found that 69% of the women had no local complications, while 31% had an implant change, implant leakage, or capsulotomy. Fewer complications were reported for women with submuscular implants and for implants having nonsmooth surfaces. The occurrence of local complications was examined among 685 Finnish women with cosmetic breast implants, with a mean follow-up of 10.9 years (range up to 34 years) (Kulmala *et al.*, 2004). Overall, 64% of women had no local complications diagnosed in their medical records. Again, the most common complication was capsular contracture, occurring in 17.7% of women and 15.4% of implants. Wound and skin problems, infection, and hematoma were diagnosed in 2.8%, 2.5%, and 1.8% of women, respectively. Seventy-four percent of women needed no postoperative treatment, while 22% required surgery after primary implantation. Breiting *et al.* (2004) conducted a study of 190 Danish women with long-term cosmetic silicone breast implants compared with 186 women who had undergone breast reduction surgery. Eighteen percent of women with implants self-reported chronic breast pain, compared with 8% among women with breast reduction. Pittet *et al.* (2005) reported that the rate of infection after silicone gel-filled breast implantation is 2-2.5%, and that two-thirds of infections occur within the acute postoperative period. The risk of infection was higher in women who had breast reconstruction after mastectomy and radiotherapy for cancer than in augmentation patients.

Thus, the epidemiologic evidence demonstrates that the incidence of short- and long-term local complications following silicone gel breast implantation is relatively low and does not typically require additional surgery. Capsular contracture is the most frequently reported complication and the most frequent cause of surgical intervention, while the frequencies of other complications such as breast pain, infection, and malposition are much lower, often as low as 1-2%. Long-term data on the newest generation of textured, highly cohesive gel implants are somewhat limited, although results from follow-up up to 11 years is consistent with a low rate of local complications.

6.4.2 Lymphoma

Concerns about non-Hodgkin lymphoma (NHL) among women with breast implants have been raised by anecdotal reports of lymphomas in or near the breast among women with breast implants (Brody *et al.*, 2010; Newman *et al.*, 2006; Gaudet *et al.*, 2002; Sahoo *et al.*, 2003; Keech and Creech 1997; Duvic *et al.*, 1995). A pooled analysis of NHL incidence in five long-term cohort studies with virtually complete follow-up of 43,537 women with cosmetic breast implants in Denmark and Sweden, the US, Canada, and Finland yielded a SIR of 0.89 (95% CI 0.67-1.18), based on 48 observed NHL cases (Lipworth *et al.*, 2009). None of the studies reported a primary lymphoma of the breast. Thus, the epidemiologic evidence, based on large surveillance studies with long-term follow-up, does not provide evidence of an increased risk of NHL of any site among women with cosmetic breast implants. In the only published cancer incidence study to include women followed for at least 25 years after implantation (Lipworth *et al.*, 2008), including 3,336 women followed for 15 years or more and 827 followed for at least 25 years, no significant excess of NHL was observed overall and not one primary lymphoma of the breast was observed. Moreover, the largest study to date (Brisson *et al.*, 2006), with cancer surveillance as long as 24 years, actually reported a reduced incidence of NHL among almost 25 000 Canadian women with cosmetic breast implants.

Recently, a report of a case-control study from the Netherlands suggested an association of breast implants with anaplastic large cell lymphoma (ALCL) (De Jong *et al.*, 2008), although the latency period between placement of the implants and ALCL diagnosis was remarkably short (< five years) for three of the five ALCLs diagnosed in implant women, weakening the plausibility that any observed association with implants is causal in nature. All the cases in this study were reported to be patients with ALCL of the breast

identified in the Netherlands between 1990 and 2006, while all of the controls had lymphomas of the breast but of cell types other than ALCL diagnosed during the same time period. Thus, the elevated odds ratio presented in the paper does not demonstrate an increased risk of ALCL of the breast among augmented women per se. In fact, no valid conclusion at all can be drawn regarding whether there is an excess of lymphoma overall, or of ALCL in particular, among women with breast implants compared with women without implants, since control patient selection purposefully comprised only patients with breast lymphomas other than ALCL. Of interest, all five of the women with ALCL and breast implants had bilateral "saline-filled" implants, which are used infrequently in Northern Europe, where silicone breast implants have not been taken off the market as they were in North America. Thus, the only valid conclusion that can be drawn from this study is that among women with breast lymphomas in the Netherlands, those whose pathology is of the anaplastic, large cell type variety may be more likely to have received saline implants (Lipworth *et al.*, 2009).

Lymphomas of the breast are rare, comprising 0.04-0.5% of all breast cancers (Kim *et al.*, 2011a, 2011b), and the vast majority of are B-cell origin. Anaplastic large cell lymphoma is a rare type of lymphoma, or cancer of the immune system, characterized by abnormal growth of T-lymphocytes that occurs in several parts of the body, including lymph nodes, skin (cutaneous ALCL), breast, bones or soft tissue. ALCL is not cancer of the breast tissue. Rather, implant-associated ALCL falls within a broad spectrum of lymphoproliferative disorders with variable clinical behaviors, raising questions about a diagnosis of malignancy in many instances (Jewell *et al.*, 2011). According to the United States National Cancer Institute, approximately 1 in 500,000 women is diagnosed with ALCL in the United States each year, with ALCL in the breast even less common, diagnosed in 3 in 100 million women per year (FDA, 2011). In 2011, an FDA summary of the literature through May 2010 identified at least 34 unique cases of ALCL among women with breast implants, and concluded that women with breast implants may have a very small but increased risk of developing ALCL in the scar capsule adjacent to the implant (FDA 2011). Of the 34 cases, the median time from breast implantation to ALCL diagnosis was 8 years (range 1-23 years), and ALCL in women with breast implants is generally located in the region immediately surrounding the breast implant (seroma or fibrous capsule) but without invasion of the breast parenchyma. Most ALCL patients were diagnosed at the time of medical treatment for complications such as persistent seromas, capsular contracture or peri-implant masses. The evidence on implant characteristics, in particular implant surface, is too limited to evaluate whether implants with textured or smooth outer shell are associated with ALCL. As stated by the FDA, "the totality of the evidence continues to support a reasonable assurance that FDA-approved breast implants are safe and effective when used as labeled."

Several independent reviews of the literature pertaining to ALCLs among women with breast implants have been published (Kim *et al.* 2011b; Jewell et al, 2011; Brody *et al.* 2010). In a review of 36 clinical cases of NHLs involving the breast among women with implants, 29 were ALCLs (Kim *et al.*, 2011b). However, 12 of the 29 women with ALCLs had a prior history of cancer other than T-cell lymphoma and two had a prior history of T-cell lymphoma. Similarly, Brody *et al.* (2010) identified 34 cases of T-cell ALCL among women with breast implants, all presenting as late peri-implant seromas, capsular contracture or peri-capsular tumor masses. The authors obtained preliminary data on brand and style of implant for 25 of the cases, and reported that 23 of them had a specific textured surface created by the lost salt method. Most if not all of these cases likely overlap with those reviewed by the FDA.

In summary, a potential association between ALCL and breast implants in general, or implants with particular characteristics such as a textured shell in particular, has been suggested by anecdotal reports of small numbers of women. A causal link between breast implants has not been established, nor has an association been evaluated in a large, well-designed epidemiologic study to date.

6.4.3 Other forms of cancer

More than a dozen epidemiologic studies, many of which have been large and able to assess long-term risks, have been conducted in North America and Europe to evaluate the potential association between cosmetic breast implants and the incidence of breast and other cancers (Breiting *et al.*, 2004; Gabriel *et al.*, 1994; Brinton *et al.*, 1996,2000a,2001a; Bryant and Brasher, 1995; Deapen *et al.*, 1997; Kern *et al.*, 1997; Malone *et al.*, 1992; Park *et al.*, 1998; McLaughlin *et al.*, 1998,2006; Mellemkjaer *et al.*, 2000; Pukkala *et al.*, 2002; Friis *et al.*, 2006; Brisson *et al.*, 2006; Lipworth *et al.*, 2008). There are no data available specifically on the incidence of cancer among recipients of PIP silicone breast implants.

The primary concern among breast implant patients, the medical community, and regulatory agencies was breast cancer risk because of the location of the implants, their use for reconstruction following breast cancer, and the hypothesis that they may interfere with mammographic detection of breast cancer. Some early reports also raised concern that women with silicone gel-filled breast implants may be at increased risk of developing other cancers, including lung cancer, cancers of the cervix and vulva, leukemia, and multiple myeloma. However, epidemiologic studies have been remarkably consistent in finding no evidence of increased breast cancer risk among women with breast implants, and the weight of the epidemiologic evidence is consistent with there being no causal association between breast implants and any other type of cancer. Accordingly, independent scientific reviews have unanimously concluded that there is no demonstrated excess of cancer of any type among women with silicone breast implants (Bondurant *et al.*, 1999; McLaughlin *et al.*, 2007; EQUAM, 2000; International Agency for Research on Cancer, 1999; National Institutes of Health, 2005). Indeed, in 1999, the International Agency for Research on Cancer (IARC) took the unusual step of concluding that there was evidence of a lack of breast carcinogenicity in women with silicone breast implants, and this conclusion was supported by that of the independent report of the IOM Committee on the Safety of Silicone Breast Implants (Bondurant *et al.*, 1999).

Numerous epidemiological studies have continued to evaluate risk of breast and other cancers in women with silicone gel-filled breast implants. In a pooled analysis of the two large Scandinavian, nationwide cohort studies with virtually complete follow-up and cancer ascertainment (Lipworth *et al.*, 2008), 3486 Swedish women (McLaughlin *et al.*, 2006) and 2736 Danish women (Friis *et al.*, 2006) who received cosmetic implants between 1965 and 1993 were followed for up to 37 years, with more than half followed for 15 years or more. There was no statistically significant increase in cancer incidence overall, compared with the general population of age-matched women. Similarly, Pukkala *et al.* (2002) conducted a cohort study of 2171 Finnish women with cosmetic breast implants, with a mean length of follow-up of 8.3 years. Cancer incidence overall was similar to that expected in the general population. Brinton *et al.* (1996,2000a) conducted a retrospective cohort study of the incidence and mortality of cancers of various types among 13 488 women with silicone breast implants compared with 3936 women who had other types of plastic surgery as well as with women in the general population. There was a slight excess of cancer incidence overall among women with implants (SIR=1.2; 95% CI 1.1-1.4) when compared with women in the general population, but not when compared with other plastic surgery patients (Brinton *et al.*, 2000a). In the large Canadian cohort study, the incidence rate for cancer at all sites combined was significantly reduced among 24 558 women with implants compared with the general population (SIR=0.75; 95% CI 0.70-0.81) and was similar to that among other plastic surgery patients (Brisson *et al.*, 2006).

The incidence of breast cancer was below expectation in virtually all the large-scale epidemiologic studies, with risk ratios suggesting a reduction of 10-50%. In the pooled Scandinavian study (Lipworth *et al.* 2008), there was a significantly reduced incidence of breast cancer among women with implants, with 84 cases observed compared with 115.62 expected (SIR=0.73; 95% CI 0.58-0.90). The combined mean duration of follow-up among all women with implants was 16.6 years (range 0.1-37.8 years). Over 50%

(n=3,280) of women in the cohort were followed for 15 years or more after implantation, and 13.2% (n=824) were followed for at least 25 years. When the SIR for breast cancer was evaluated stratified by time since breast implantation, breast cancer SIRs were non-significantly reduced throughout the follow-up period. The corresponding SIR for breast cancer in the large Canadian study was 0.57 among 24,558 women with implants (Brisson et al, 2006). The consistently observed reduced incidence of breast cancer among women with breast implants may be explained by a higher prevalence of patient characteristics which may put them at a lower risk for breast cancer, including younger age at first birth, higher parity and lower body mass index (Kjoller et al, 2003; Cook et al, 1997; Fryzek et al, 2000; Brinton et al, 2000b). Most studies of cancer among women with breast implants did not have information on reproductive characteristics of the particular women included in the study. However, in a separate analysis of the Danish women with implants included in the pooled Scandinavian study, the reduction in breast cancer risk persisted even after adjustment for age at first birth and number of children (Friis et al, 2006), suggesting that reproductive factors may not have a major influence. It is also plausible that women seeking cosmetic breast implantation may be diagnosed with breast cancer during preoperative screening. Exclusion of these women whose breast cancers would have ultimately been diagnosed during follow-up could lead to decreased incidence of breast cancer among women with cosmetic breast implants compared with women in the general population, although these effects are unlikely to explain the persistent risk reduction with long-term follow-up.

The IOM (Bondurant *et al.*, 1999) suggested that implants may make screening mammography more challenging by obscuring a variable part of breast tissue. Based on the findings of a few case series (Fajardo *et al.*, 1995; Silverstein *et al.*, 1988, 1990, 1992), many originating from the same clinic, a hypothesis was generated that opaque breast implants may interfere with physical breast examination or mammographic visualization of breast tumors, leading to delays in breast cancer diagnosis and worse prognosis among women receiving implants. However, the interpretation of these clinical case series is hampered by potential referral or ascertainment bias, small sample size and absence of a control group. Furthermore, many of the women included in these case series underwent their mammograms prior to the implementation of Eklund's implant displacement technique which improved the accuracy of mammograms for women with breast implants (Eklund *et al.*, 1988), although a portion of the breast may still not be adequately visualized.

Numerous epidemiologic studies have evaluated whether implants delay the detection of breast cancer by comparing the stage distribution among women with implants at breast cancer diagnosis with an appropriate comparison group. Virtually all of these studies indicate that, although the sensitivity of mammography may be reduced somewhat in women with breast implants, these women do not in fact present with more advanced stages of breast cancer or suffer from reduced survival after breast cancer diagnosis (Friis *et al.*, 2006; McLaughlin *et al.*, 2006; Deapen *et al.*, 2000; Hoshaw *et al.*, 2001; Miglioretti *et al.*, 2004; Holmich *et al.*, 2003c). Most recently, Xie *et al.* (2010) reported on stage distribution and prognosis among 182 and 202 incident cases of breast cancer identified in the large Canadian cohorts of women with breast implants and women with other plastic surgery procedures. Women with breast implants were more likely to be diagnosed with a more advanced stage of breast cancer compared with other plastic surgery patients. However, there were no differences in tumor size and breast cancer-specific survival was similar in both groups. Moreover, none of the mortality studies to date has demonstrated an increased risk for death from breast cancer among women with implants compared with women in the general population (Lipworth *et al.*, 2007; Jacobsen *et al.*, 2004; Brinton *et al.*, 2006; Villeneuve *et al.*, 2006).

Few statistically significantly increased or decreased SIRs were observed for other types of cancers in any of the studies. A significant increase in lung cancer (SIR=2.2; 95% CI 1.3-3.4) was observed among women with implants in the Swedish study (McLaughlin *et al.*, 2006). An earlier survey based on a randomly selected subset of these Swedish women with breast implants found that they were 2.8 times more likely to be current

smokers than the general population of Swedish women (Fryzek *et al.*, 2000). This difference in smoking habits is likely to explain the increase in lung cancer risk among women in this study, as well as the excess of lung cancer mortality among women with breast implants in a Swedish mortality study (Lipworth *et al.*, 2007). The slight excess of total cancer in the study by Brinton *et al.* (2000a) was due primarily to statistically significant increased risks of cervical, vulvar, and brain cancer, and leukemia compared with the general population. Substantial differences in demographic, lifestyle, and/or reproductive characteristics between women with implants and both women with other types of cosmetic surgery and women in the general population have been reported in several epidemiologic studies (Fryzek *et al.*, 2000; Kjoller *et al.*, 2003; Cook *et al.*, 1997; Brinton *et al.*, 2000b) and are likely to account for these sporadic excesses of cancer, in particular vulvar, cervical and lung cancer.

Brain cancer has been studied quite extensively in several large-scale incidence studies (Pukkala *et al.*, 2002; Friis *et al.*, 2006; McLaughlin *et al.*, 2006; Brisson *et al.*, 2006; McLaughlin and Lipworth, 2004), as well as in five mortality studies (Lipworth *et al.*, 2007; Jacobsen *et al.*, 2004; Brinton *et al.*, 2001b,2006; Pukkala *et al.*, 2003; Villeneuve *et al.*, 2006), all of which consistently failed to demonstrate any significant excess among women with cosmetic breast implants. Only one study to date has reported a significant excess of brain cancer among women with breast implants (Brinton *et al.*, 2001b), but upon further follow-up no additional deaths from brain cancer were observed (Brinton *et al.*, 2006), yielding a non-significant standardized mortality ratio (SMR) of 1.4 (95% CI 0.8-2.5) after an average of 20 years of follow-up.

In summary, the results of the most recent investigations are remarkably consistent with earlier epidemiologic evidence in demonstrating no credible evidence of a causal association between breast implants and any type of cancer, including cancer of the breast.

6.4.4 Other effects

Rupture of silicone breast implants has anecdotally been associated with severe symptoms. Subsequent to trauma or closed capsulotomy, episodes of transcutaneous or intraductal extension of silicone from a ruptured implant have been described, (Ahn and Shaw 1994, Leibman *et al.*, 1992) as has distant migration of free silicone via facial planes (Huang *et al.*, 1978, Teuber *et al.*, 1999) and alarming growth in silicone granulomas, probably representing rare runaway foreign body reactions, resulting in devastating tissue excisions (Teuber *et al.*, 1999, Malyon *et al.*, 2001). Such events are rare, although most clinicians with several years in practice have knowledge of a case or two. No studies have quantified the frequency of occurrence of these events.

To date, only one prospective study has addressed the possible health implications of ruptured, *in situ* silicone breast implants. In this unique study, Holmich and colleagues (2004) examined the possible health implications, including changes over time in MRI findings, serological markers, or self-reported breast symptoms, of untreated silicone breast implant ruptures. Sixty-four women with implant rupture diagnosed by MRI were followed for two years, and a second MRI was performed. A control group of women with no evidence of rupture on either MRI was used for comparison. The majority of women had no visible MRI changes of their ruptured implants. Progression of silicone leakage (either herniation of silicone within the fibrous capsule, migration from the intracapsular space into the surrounding tissue, or progression of extracapsular silicone) was observed in 11 implants (11%) in ten women; in most cases the changes were small. There was no increase in autoantibody levels, and no increase in reported breast hardness among these women. They did report a significant increase in non-specific breast changes compared with women in the control group. The authors concluded that, for most women, rupture is a harmless condition which does not appear to progress or to produce significant clinical symptoms. Based on their findings, they concluded that routine explantation in asymptomatic women with ruptures may not be mandatory. They

recommend that asymptomatic women with implant ruptures be followed regularly by clinical examination and that the women should be informed of signs of silicone migration and in that situation explantation should be advised (Holmich *et al.*, 2004).

It has been hypothesized that women with ruptured implants may experience increased exposure to silicone, which in turn could induce an immunological reaction leading to a higher risk of specific symptoms or systemic diseases (Press *et al.*, 1992; Melmed, 1998; Solomon, 1994). As previously reviewed by Holmich *et al.* (2007), only two studies of either CTDs or related symptoms evaluated by implant rupture status were based on patients not thought to be selected by the clinical course or symptoms.

In the magnetic resonance imaging (MRI) study by Brown *et al.* (2001), 236 (68.6%) of 344 women from two volunteer plastic surgery clinics had at least one ruptured implant; 73 of these 236 women had an extracapsular rupture. Women with breast implant rupture (overall or extracapsular rupture) were no more likely than women with intact implants to self- report a diagnosis of any of the definite CTDs studied, including fibromyalgia, or symptoms including joint symptoms, skin rash, cognitive disorder, fatigue, or hair loss. When women with extracapsular silicone were compared with a combined group of women with intracapsular rupture and women with intact implants, excesses were found for self-reported Raynaud's syndrome (OR=4.2; 95% CI 1.1-16.0) and fibromyalgia (OR=2.8; 95% CI 1.2-6.3). However, there is no biologic or scientific rationale for comparing women with extracapsular rupture with a combined group of women with intracapsular rupture and women with intact implants, since women with intracapsular rupture had fibromyalgia rates substantially lower (8%) than women with intact implants (14.8%). If the analyses had been conducted appropriately, based on three separate categories of implant status (intact, intracapsular rupture, extracapsular rupture), the fibromyalgia OR for extracapsular rupture compared with intact implants would be 1.9 (95% CI 0.8-4.3), substantially lower than the 2.8 reported by the authors (Lipworth *et al.*, 2004a). Moreover, the study had considerable potential for selection bias due to recruitment procedures and low response rates, and could not determine whether self-reported conditions occurred before or after breast augmentation (Lipworth et al., 2004a).

In a sample of women from the Danish implant cohort who were randomly selected to undergo MRI to detect rupture, Holmich et al. (2003b) evaluated risk of CTD by rupture status among 238 women with cosmetic silicone breast implants. Ninety-two (39%) of the women had MRI-diagnosed ruptures, of which 69 were intracapsular and 23 were extracapsular, and 146 had intact implants. One year prior to the MRI, information was obtained on self-reported CTDs and symptoms with onset after breast augmentation. Two women in the ruptured group (both with extracapsular ruptured implants) and three women with intact implants self-reported a diagnosis of definite CTD, yielding ORs of 0.9 (95% CI 0.1-6.7) for women with ruptured implants overall and 3.8 (95% CI 0.4-35.1) for women with extracapsular ruptures compared with women with intact implants. For undefined CTD or other chronic inflammatory conditions, including fibromyalgia, the corresponding ORs were 1.0 (95% CI 0.3-3.0) and 0.8 (95% CI 0.1-4.5), respectively. Two cases of fibromyalgia were reported, one in the group with intact implants (0.7%) and one in the group with intracapsular rupture (1.4%). None of the women with extracapsular rupture reported fibromyalgia. These rates of fibromyalgia are consistent with the estimated prevalence rate of 3.4% for US women (Wolfe *et al.*, 1995), as opposed to the much higher rates of fibromyalgia reported among women with intact implants or intracapsular ruptures in the study by Brown *et al.* (2001), again suggesting biased selection of women in that study.

6.4.5 Connective Tissue Disorders (CTD)

6.4.5.1 General aspects

Initially, the primary concern regarding breast implants was the occurrence of systemic sclerosis and other connective tissue diseases (CTDs), including systemic lupus

erythematosus (SLE), rheumatoid arthritis, Sjögren's syndrome, and fibromyalgia. It had also been hypothesized that women with breast implants experience symptoms of apparent connective tissue, rheumatic, or autoimmune origin that bear some resemblance to fibromyalgia but do not fulfill established diagnostic criteria for any known CTD, including cognitive dysfunction, severe joint and muscle pain, incapacitating fatigue, and skin abnormalities (Kallenberg, 1994; Wolfe, 1999).

Although unsubstantiated claims still appear from time to time regarding an association between silicone breast implants and known or atypical CTDs, these have been unequivocally refuted by the reassuringly consistent epidemiologic evidence from published large-scale cohort (Breiting *et al.*, 2004; Brinton *et al.*, 2004; Brown *et al.*, 2001; Edworthy *et al.*, 1998; Englert *et al.*, 2001; Friis *et al.*, 1997; Fryzek *et al.*, 2007; Gabriel *et al.*, 1994; Giltay *et al.*, 1994; Hennekens *et al.*, 1996; Holmich *et al.*, 2003b; Kjoller *et al.*, 2001; Lee *et al.*, 2010; Nyren *et al.*, 1998a; Park *et al.*, 1998a; Sanchez-Guerrero *et al.*, 1995; Schusterman *et al.*, 1993; Wells *et al.*, 1994) and case-control (Burns *et al.*, 1996; Dugowson *et al.*, 1992; Englert *et al.*, 1996; Goldman *et al.*, 1995; Hochberg *et al.*, 1996; Lai *et al.*, 2000; Laing *et al.*, 1996, 2001; Strom *et al.*, 1994; Williams *et al.*, 1997; Wolfe and Anderson, 1999) studies, as well as numerous meta-analyses and critical qualitative reviews (Bondurant *et al.*, 1999; Blackburn and Everson, 1997; Hochberg and Perlmutter, 1996; Independent Review Group, 1998; Janowsky *et al.*, 2000; Lamm, 1998; Lewin and Miller, 1997; Lipworth *et al.*, 2004a,2004b,2010a; McLaughlin *et al.*, 2007; Silman and Hochberg, 2001; Silverman *et al.*, 1996; Tugwell *et al.*, 2001). Among these qualitative reviews is the US Federal court-appointed National Science Panel Report in 2001 (Tugwell *et al.*, 2001), as well as other more recent reviews (Lipworth *et al.*, 2004a,2004b,2010a; McLaughlin *et al.*, 2007) of findings from epidemiologic studies published after the National Science Panel's review, all of which have concluded that there is no credible evidence of an association between breast implants and any of the traditional CTDs evaluated individually or in combination, or atypical CTD.

6.4.5.2 Established connective tissue disease

In an early, large, well-designed epidemiologic cohort study of US female health professionals, evidence initially suggestive of a relation between well-defined CTDs and breast implants was reported (Hennekens *et al.*, 1996; Lee *et al.*, 2010). In the first analysis, there was a small but significant overall increased risk of self-reported (not validated) CTDs among women with breast implants (Hennekens *et al.*, 1996). Due to the self-reported nature of the CTD result, a subsequent medical record validation of these data was performed by the same investigators, showing clear evidence of over-reporting of CTD by the participants, as only 22.7% of self-reported cases of definite CTD could be confirmed by a review of patient records (Karlson *et al.*, 1999). In the latest update from the same study population (Lee *et al.*, 2010), initially statistically significantly elevated relative risks (RR) of 1.6-1.8 for self-reported CTDs or for CTDs ascertained using a specialized CTD screening questionnaire (CSQ) were again found to be greatly attenuated and no longer significant when the analysis was restricted to CTD cases confirmed by medical records. Among women with implants, CTD diagnoses were confirmed for only 27% of women who screened positive for CTD on the CSQ, and for 18% of women who self-reported a CTD. The most informative result of this study, therefore, is the high level of CTD over-reporting by women with implants, particularly among US women with implants when there was nationwide litigation, sensational media reports, and a government de facto ban of the use of silicone-filled cosmetic breast implants. For most other industrialized countries, this was not the environment.

Over-reporting was similarly evident in a US cohort study (Brinton *et al.*, 2004) of 7234 women with breast implants, in which only a small minority of self-reports of rheumatoid arthritis, scleroderma and Sjogren's syndrome were considered "likely" (i.e., likely real) after medical record review by a panel of expert rheumatologists. For the remainder, the diagnoses were not supported, either because records were incomplete or because

clinical criteria were not met. Based on these "likely" diagnoses, RRs among women with implants were non-significantly elevated for the three disorders combined (RR=2.5; 95% CI 0.8-7.8) or for rheumatoid arthritis alone (RR=1.9; 95% CI 0.6-6.2). The US study also found that women with breast implants were not more likely to have fibromyalgia than women with other types of plastic surgery, based on self-reports (RR=1.3; 95% CI 0.9-1.7).

In a study of Danish women (Breiting *et al.*, 2004) with long-term follow-up up to 35 years after implantation, no significant association for all CTDs combined was reported among 190 women with cosmetic silicone breast implants when compared with either 186 breast reduction controls (RR=0.8) or 149 women in the general population (RR=1.4). This study was able to identify women who had received their implants on average almost two decades earlier, but due to the relatively small sample size had limited statistical power to observe associations with rare outcomes such as individual CTDs.

Fryzek *et al.* (2007) reported on the occurrence of CTD in an extended follow-up of an earlier study of 2761 Danish women with breast implants and 8807 comparison women who underwent breast reduction surgery (Kjoller *et al.*, 2001). The women with implants were followed with virtually complete follow-up for an average of 13.4 years, and all CTD outcomes were based on hospital records and were medically verified through medical chart review to evaluate possible misclassification of these diseases at discharge in the study cohorts. Over 85% of CTDs diagnosed in hospital records were confirmed through medical chart review for women with breast implants. Compared with either general population rates or with women with breast reduction, women in the implant cohort had no significant increase in the incidence of combined CTDs or of any specific CTD, including rheumatoid arthritis, dermato- and polymyositis, systemic sclerosis, SLE, and Sjögren's syndrome. Direct comparison of the implant and comparison cohorts showed no relation for breast implants with confirmed fibromyalgia.

Nyren *et al.* (1998a) conducted a large Swedish cohort study that included 3500 women with cosmetic breast implants, followed for a mean of 10.3 years, and 3353 women with breast reduction followed for a mean of 9.9 years. This study relied on a medical record data review to correct for all misclassified and pre-existing (prevalent) CTD diagnoses in both cohorts. In a direct comparison with women who had undergone breast reduction, the RR for hospitalization for total CTDs was 0.8, and no significant increases were found among women with breast implants for any specific CTD, including rheumatoid arthritis, SLE, Sjogren's, or scleroderma. The RR for fibromyalgia among women with breast implants was 1.0 (95% CI 0.3-3.0) compared with women who had undergone breast reduction.

Englert *et al.* (2001) conducted a retrospective cohort study in Australia of 458 women who received cosmetic breast implants between 1979 and 1983 and 687 women with other types of plastic surgery. Diagnoses of CTDs subsequent to implantation or other plastic surgery were self-reported and then validated through medical record review. There was no statistically significant difference between women with breast implants and controls in the reporting of any CTD or of systemic sclerosis, SLE, or rheumatoid arthritis.

With respect to fibromyalgia, a case-control study by Wolfe and Anderson (1999) found no association between silicone breast implants and the subsequent development of fibromyalgia. Utilizing a longitudinal clinical databank of patients seen at a rheumatic disease clinic from 1991 through 1994, history of breast implantation (including date of implantation) was ascertained among 508 women with fibromyalgia, as well as among 464 women with rheumatoid arthritis and 261 rheumatic disease controls with osteoarthritis. The fibromyalgia patients were the least likely to have had breast implantation prior to their diagnosis. When women with fibromyalgia were compared with women with osteoarthritis, who were selected by the investigators to serve as the relevant disease control group, the odds ratio (OR) for fibromyalgia diagnosed after implantation was 0.77 (95% CI 0.13-4.65), highlighting the importance of determining,

in studies of breast implants, whether self-reported CTDs or symptoms occurred before or after breast augmentation surgery.

Similarly, Lai *et al.* (2000) conducted a case-control study of women seen at a rheumatology practice in Atlanta from 1986 through 1992 to ascertain prior history of breast implantation and fibromyalgia. Medical records were reviewed for 2500 women, of whom 131 had a history of breast implantation and 484 met the American College of Rheumatology criteria for fibromyalgia. There was no association between breast implantation and fibromyalgia.

In addition to the studies reported above, a number of earlier cohort studies, most with shorter follow-up and fewer study subjects, also found no increased risk of definite CTDs among women with cosmetic breast implants when compared with either women who had undergone breast reduction or women in the general population, although the relatively small numbers of rare outcomes such as specific CTDs reported in these studies often precluded meaningful comparisons. Included among these early studies are the "Mayo Clinic Study" of 749 women in Minnesota, who received silicone breast implants between 1964 and 1991 and were followed for an average of 7.8 years (Gabriel *et al.*, 1994); a study of 1183 women with breast implants identified from the Harvard Nurses' Health Study cohort (Sanchez-Guerrero *et al.*, 1995); and a nationwide Danish Hospital Discharge Register study (Friis *et al.*, 1997) of 1135 women with cosmetic breast implants.

6.4.5.3 "Atypical" connective tissue disease

Studies that evaluated undifferentiated or atypical CTD as an outcome, defined as having a case definition distinct from the other established CTDs and substantive symptoms (Williams *et al.*, 1997), have consistently reported no credible evidence of an association with silicone breast implants or of a rheumatic symptom profile unique to these women and/or indicative of a specific atypical CTD (Bondurant *et al.*, 1999; Breiting *et al.*, 2004; Brinton *et al.*, 2004; Fryzek *et al.*, 2001a, 2007; Jensen *et al.*,2001a, 2001b; Kjoller *et al.*, 2001; Laing *et al.*, 2001; Lipworth *et al.*, 2004b, 2010a; Tugwell *et al.*,2001).

In the Danish follow-up study (Fryzek *et al.*, 2007), unspecified rheumatism (which included fibromyalgia and myalgia) was statistically significantly elevated in both the implant cohort (standardized incidence ratio (SIR)=1.9; 95% CI 1.6-2.2) and in the comparison cohort of 8,807 women who underwent breast reduction surgery (SIR=1.5; 95% CI 1.4-1.7) cohorts, when compared with the general population. A validation of the diagnosis "unspecified rheumatism" (Jensen *et al.*, 2001b) did not reveal a rheumatic symptom profile unique to women with silicone breast implants or suggestive of atypical CTD. Jensen *et al.* (2001a) examined rheumatic diagnoses and related symptoms among women with implants with and without a prior diagnosis of muscular rheumatism, and observed that the frequency of fibromyalgia and the number of tender points were markedly increased among women with earlier muscular rheumatism compared with women without a prior diagnosis of muscular rheumatism. These results, again, indicate the importance of taking prior rheumatic complaints and diseases into consideration when evaluating current rheumatic diseases among women with breast implants.

In the US study of CTDs by Brinton *et al.* (2004), the authors included a category of self-reported conditions termed "other disorders." The RR for these self-reported disorders among women with implants compared with other plastic surgery controls was 1.4 (95% CI 0.8-2.6) for the period before 1992 and 3.6 (95% CI 1.9-7.0) for the period after 1992, during which breast implant litigation and media reports were widespread in the United States, suggesting strong reporting bias inherent in these self-reports of CTDs during a period of widespread litigation and publicity. Moreover, the authors indicate that most of these "other CTDs" were "vaguely defined or should not have been considered CTDs."

In the largest study to date to examine symptom reporting for a pattern unique among breast implant recipients (Fryzek *et al.*, 2001a), 1546 Swedish implant patients and 2496 breast reduction controls completed a questionnaire regarding rheumatologic and other symptoms. Women with breast implants reported a multitude of symptoms, but with a clear lack of specificity. Thus, after extensive cluster analysis, there was no identifiable cluster of symptoms indicative of a specific "atypical" CTD, nor was there a unique pattern of inflammatory rheumatic disorders or soft-tissue complaints among women with silicone breast implants.

6.4.6 Offspring effects

There are no epidemiologic data available on offspring effects among women with PIP silicone breast implants. However, there have been several well-conducted, long-term studies of offspring effects among women with implants dating back to the 1990's.

There were isolated early case reports of children born to or breastfed by women with silicone breast implants who developed swallowing difficulties, irritability, nonspecific skin rashes, fatigue, and other symptoms (Gedalia *et al.*, 1995; Levine and Ilowite, 1994; Levine *et al.*, 1996a,1996b,1996c; Teuber and Gershwin, 1994). Besides the lack of a control group in these case series or small clinical studies, selection bias is a major concern due to the referral of children to a gastroenterology clinic because of a concern about breast implants, including those whose mothers were involved in implant litigation (Bartel, 1994; Cook, 1994; Epstein, 1994; Placik, 1994). In addition, some of the children were born to families with a history of scleroderma and esophageal dysmobility, so genetic or familial factors cannot be ruled out, and sedation of the children during testing may have affected oesophageal pressures.

Four population-based retrospective cohort studies have examined health outcomes among children born to mothers with silicone breast implants, and none has found evidence of such a relationship.

Kjoller *et al.* (1998) examined the occurrence of oesophageal disorders, connective tissue diseases (CTD), and congenital malformations among 399 Danish children of mothers who received breast implants at public hospitals between 1977 and 1992, compared with 3906 children of mothers who had undergone breast reduction. After a mean follow-up of 5.5 years (range up to 15.7 years), higher than expected rates of oesophageal disorders were found among children born to mothers with implants, compared with the general population; however, similar excesses were observed among the control group of offspring born to mothers with breast reduction surgery, and excesses were also observed among children born prior to the mother's implant surgery. The observation of an increased occurrence of oesophageal disorders among the offspring of women with implants both before and after implant surgery, and women with breast reduction suggests confounding by some characteristics of women who undergo cosmetic breast operations in general as a likely explanation for the observed excesses. There were no significant increases in CTD or congenital malformations in either the breast implant or breast reduction cohorts.

Kjoller *et al.* (2002a) reported on an additional cohort of children of Danish women who received implants at private plastic surgery clinics between 1973 and 1995, and updated the follow-up of the earlier public hospital implant and reduction cohorts (Kjoller *et al.*, 1998). The mean follow-up after breast implantation for the private clinic and public hospital cohorts combined was 6.0 years (range up to 19 years). Esophageal disorders, rheumatic disease, and congenital malformations were examined among 2854 children born to Danish women with implants and 5805 children born to women who underwent breast reduction or other plastic surgery. Significantly higher than expected rates of esophageal disorders were observed for children born before (SIR=2.0; 95% CI 1.3-2.8) but not after (SIR=1.3; 95% CI 0.5-2.9) maternal implant surgery; similar excesses were observed among children born before (SIR=2.1; 95% CI 1.5-2.8) and after (SIR=1.6; 95% CI 1.1-2.3) maternal breast reduction surgery. Risks of rheumatic

disease were not significantly elevated and were similar among children born before and after maternal breast implant surgery. A borderline significant excess of congenital malformations of the digestive organs was observed among children born after maternal implant surgery (SIR=1.8; 95% CI 1.0-3.1), but a similar excess was observed among children born to women in the breast reduction cohort after their surgeries (SIR=1.9; 95% CI 1.4-2.4). The risk of malformations overall was not significantly higher than expected among children born after cosmetic breast surgery. Any observed elevated risks of adverse health outcomes appear unrelated to breast implants per se, because similar findings were observed among children born both before and after the mother's implant surgery, as well as among children born to control mothers in the breast reduction cohort.

Similarly, a retrospective cohort study conducted in Sweden found no evidence of increased risk of adverse health outcomes among children born to women with breast implants, after a mean follow-up of 8.9 years (range up to 24 years) (Signorello *et al.*, 2001). The investigators evaluated hospitalization rates for rheumatic and esophageal disorders, incidence rates for cancer, and prevalence rates for congenital malformations among 5874 children born to women with cosmetic breast implants compared with 13 274 children born to women who had undergone breast reduction surgery. Compared with children of women who had undergone breast reduction, children of women with cosmetic breast implants were not at increased risk for rheumatic disease (RR=1.1; 95% CI 0.2-5.3), esophageal disorders (RR=1.0; 95% CI 0.7-1.6), congenital malformations overall (RR=1.0; 95% CI 0.6-1.5), congenital malformations specifically involving the digestive organs (RR=0.5; 95% CI 0.2-1.3), cancer (RR=0.3; 95% CI 0.0-2.5) or perinatal death (RR=0.9; 95% CI 0.5-1.8).

A fourth study, conducted in Finland (Hemminki *et al.*, 2004), attempted to evaluate perinatal health outcomes among infants born to women with silicone breast implants, as well as pregnancy and birth patterns among these women. In general, this study suffered from numerous methodological shortcomings, including biased control selection and uncontrolled confounding. As a result of these flaws the null results are uninterpretable.

In summary, there are no demonstrated adverse effects on the offspring of women with breast implants.

6.4.7 Suicide and psychological issues

Five large epidemiologic mortality studies, conducted in various populations during the past decade, have reported with remarkable consistency that women with cosmetic breast implants have a two- to three-fold higher rate of suicide than similar-aged women in the general population (Lipworth *et al.*, 2007; Jacobsen *et al.*, 2004; Brinton *et al.*, 2001,2006; Pukkala *et al.*, 2003; Villeneuve *et al.*, 2006). To our knowledge, prior to these mortality studies, there were no case reports or case series in the literature to suggest a suicide excess among women with cosmetic breast implants. It was an unexpected finding and the only adverse outcome consistently observed in the epidemiologic studies of women with implants. There are no epidemiologic mortality studies or studies of psychological characteristics of women specifically with PIP silicone breast implants.

Three nationwide cohort studies have been conducted in Scandinavia to evaluate cause-specific mortality among women with breast implants. In the Swedish cohort of 3521 women who had breast implants and were followed for an average of 18.7 years (up to 38 years) after implantation, a statistically significant threefold excess rate of suicide compared with the general population was observed base on 24 deaths (SMR=3.0; 95% CI, 1.9–4.5). The excess rate of suicide in this study became apparent 10 years after implantation and continued to increase with extended follow-up to an SMR of 4.5 (95% CI, 2.6–7.7) among women ten to 19 years after implantation and 6.0 (95% CI, 2.7–13.4) among women 20 or more years after implantation (Lipworth *et al.*, 2007).

Jacobsen *et al.* (2004) reported an increased risk of suicide (SMR = 3.1; 95% CI 1.7-5.2), based on 14 observed suicides compared to an expected 4.5 in the Danish implant cohort of 2788 women with implants, with a mean follow-up of 11.5 years (range, 4-26 years). No clear pattern emerged in the SMRs for suicide according to length of follow-up, with substantial excesses observed in all time periods. This was the first and to date only mortality study to explore pre-implant psychopathology among women undergoing cosmetic breast implant surgery, by examining their pre-operative history of hospitalization for psychiatric illness. The results of this study indicate that the Danish women who underwent breast implantation had a higher prevalence of psychiatric admissions prior to cosmetic surgery (8.0%; 95% CI 7.0%-9.0%) than women who underwent breast reduction (4.7%; 95% CI 4/2%-5.2%) or other types of cosmetic surgery (5.5%; 95% CI 4.5%-6.7%). When compared with all control groups, the risk ratio for prior psychiatric admission was 1.7 (95% CI 1.4-2.0). In fact, seven of 14 women with breast implants who committed suicide in the study had a history of pre-operative psychiatric hospitalization. The study did not, however, provide information on history of specific psychiatric diagnoses or treatments prior to breast implantation.

Brinton *et al.* (2006), in their mortality analysis for the US cohort of 12 144 women who received cosmetic breast implants, reported an increased risk of suicide among implanted women when compared with the general population (SMR = 1.6; 95% CI 1.1-2.3, based on 29 observed suicides) or when compared with other cosmetic surgery patients (RR = 2.6; 95% CI 0.9-7.8). The risk of death from suicide was not elevated during the first ten years of follow-up but was increased in all subsequent time periods.

In the mortality analysis of the large Canadian cohorts (Villeneuve *et al.*, 2006), significantly higher rates of suicide were observed in both the implant (SMR=1.7; 95% CI 1.3-2.2) and other plastic surgery groups (SMR=1.6; 95% CI 1.1-2.2) compared with the general population, based on 58 and 33 observed suicides, respectively. In the Finnish cohort of 2166 women who had cosmetic breast implantation and were followed for a mean of 10.3 years (Pukkala *et al.*, 2003), a statistically significantly increased SMR for suicide was observed among implanted women compared with the general Finnish female population (SMR = 3.2; 95% CI 1.53-5.86, based on 10 suicides compared to an expected 3.1).

In addition to the increased risk of suicide among women with cosmetic breast implants, excesses of other external causes of deaths due to drug and alcohol abuse and dependence, atypical motor vehicle accidents, and other self-harm causes were also reported in the five published mortality studies (Lipworth *et al.*, 2010). The consistently higher rate of suicide, as well as the observed excesses of other drug- and alcohol-related external causes of death, among women with cosmetic breast implants is unlikely to represent a causal association, but rather reflects an increased prevalence of preexisting underlying psychiatric problems and other important risk factors for suicide among a subset of these women prior to their implantation. However, direct empirical research on these women prior to surgery for cosmetic implants is limited.

Women with cosmetic breast implants have been shown to have a higher prevalence of cigarette smoking and alcohol use, younger age at first pregnancy, history of induced abortions, and lower-than-average body weight (Fryzek *et al.*, 2000; Kjoller *et al.*, 2003; Cook *et al.*, 1997; Brinton *et al.*, 2000; Didie and Sarwer 2003), perhaps reflecting an increased prevalence of eating disorders among a subset of these women. Moreover, there is some evidence that women who seek cosmetic breast implantation experience preoperative psychological symptoms indicative of depressive disorders or report a history of psychiatric treatment substantially more frequently than women undergoing other cosmetic surgery (Didie and Sarwer 2003; Sarwer *et al.*, 2000, 2003; Young *et al.*, 1994). These and other characteristics may influence rates of suicide and related causes of death. The prevalence and severity of pre- and post-implant psychiatric disorders or other factors needs to be further investigated to identify whether some women who undergo cosmetic breast implantation are at high risk of suicide.

There are no studies of PIP silicone breast implants and suicide and related causes of death. However, if women with PIP silicone breast implants are similar in psychological characteristics as women with implants in general, then an excess of suicides and related causes of death would be expected.

6.4.8 Case reports on women with PIP Breast implants

Incident reports collected by the International Confederation for Plastic Reconstructive and Aesthetic Surgery network from Spain, France, UK, Finland, Lebanon, Czech Republic, Italy, Switzerland have raised concerns about unusually high rupture rates in PIP silicone breast implants and lymphadenopathy (with swellings, pain and inflammation), including in lymph nodes far away from the breast, *e.g.*, in the groin, in the neck and in the mediastinum. These lyphadenopathies do not seem to subside after implant removal and can develop even with intact implants. Such a case on lymphadenopathy at a site distant from the implant manifesting itself as cutaneous abnormalities was recently reported for a patient with a PIP implant (Cawrse and Pickford 2011).

No epidemiologic data are available regarding local complications of any kind following implantation with PIP silicone breast implants. If local complication rates of PIP silicone breast implants are similar to other manufacturers' implants, then the issue is likely to be of relatively minor importance in terms of risk to the public health. In a small study on eight explanted PIP silicone breast implants three intracapsular ruptures were identified of which two were symptomatic (Carillon *et al.*, 2012).

No scientific data are available regarding the occurrence of lymphoma of any kind, including ALCL, following implantation with PIP silicone breast implants.

No epidemiologic data on PIP silicone breast implants are available regarding the subsequent occurrence of cancer, including breast cancer. If PIP silicone breast implants are like other implants in regards to subsequent cancer, no association would be expected.

There are no offspring studies of women with PIP silicone breast implants.

There are no studies of PIP silicone breast implants and suicide and related causes of death. However, if women with PIP silicone breast implants are similar in psychological characteristics as women with implants in general, then an excess of suicides and related causes of death would be expected

6.5 Risks related to surgical procedures for breast implantation and explantation

6.5.1 Implant procedure risks

It has been shown in different studies that implant damage at insertion can weaken the implant and probably be responsible, at least in part for a later rupture. Electron microscopy scanning studies of failed implants have shown various types of failure mechanisms, from scalpel, scissor, needle and forceps lesions to abraded, weakened areas, probably caused by surgeons' fingers when they are stuffing an implant into its pocket (Rapaport *et al.*, 1997, Brandon *et al.*, 2001, Wolf *et al.*, 2000).

It should be noted that in many countries a considerable amount of aesthetic breast surgery is done by non-specialized physicians, who frequently do not even have had any training in basic surgery (*e.g.* Germany). A substantial proportion of the procedures in aesthetic breast surgery are estimated to be done by non-specialists. It is not clear whether this lack of suitable training has a major influence on subsequent breast implant failure rates.

6.5.2 Infection risks

According to the literature, infections are not numerous in the possible complications of breast reconstruction or breast augmentation. They could appear early or be detected as subclinical in the pathogenesis of fibrous contracture.

The early infectious complications after nipple-sparing mastectomy and immediate breast reconstruction with silicone prosthesis are recorded for 5% (2% major infection and 3% minor infection) of the 16% complications in the prospective study of Radovanovic *et al.* (2010). In the study of Siggelkow *et al.* (2004) dedicated to breast implant for cosmetic augmentation or breast reconstruction, the percentage of complication is significantly of higher incidence in patients who had undergone breast reconstruction but still very low («3%).

Some of these early infectious complications could include a Toxic Shock Syndrome linked to toxicogenic *Staphylococcus aureus* and have a dramatic issue if an early diagnosis and prompt initiation of resuscitative and therapeutic measures are not present. But they occur very rarely (Holm & Mühbauer 1998).

Much more frequent is the subclinical infection detected when a reintervention occurs for capsule contracture. They seem to be the source of this contracture in around 30% of the cases and are linked to a biofilm with *Staphylococcus epidermidis* on the breast implant capsule (Pajkos *et al.*, 2003). They need sensitive culture methods for being detected (swabbing is insufficient). For avoiding this phenomenon some surgers are carefully disinfecting the implant before introduction (immersion in a disinfecting solution or antibiotics) and a debate about the role of an eventual interaction between this disinfectant and the membrane of the implant seems to be now closed in the USA (Zambacos *et al.*, 2004).

Meanwhile we may question about an eventual fragility of the shell of PIP silicone breast implants after contact and interaction with a disinfectant if this was not tested before marketing and specified in the notice. This could an eventual cause of more rapid disorders as usual but the data now recorded did not contain any information about this practice and the habits of surgers seem dissimilar.

There were no papers found in the literature dealing with infections linked to contaminated silicone exuding out of the membrane. There are some cases described of granulomas linked to atypical mycobacteria , but all the patients where HIV positive and the source of the bacteria seems to be external and not directly linked to the silicone (Males *et al.*,2010).

No papers were found showing a difference in infections rates between PIP and other protheses. On the other hand one author described recently a zero breast implant infection rate following 1720 PIP silicone implant placements for primary breast augmentation (Keramidas 2009).

No possible microbiological contamination of PIP breast implants was found in the literature. The non-medical silicones are not marketed as "germ free" , thus it could be assumed that the initial contamination of PIP implant may be higher than in the case of implants filled with a certified medical silicone . According to this hypothesis, the applied sterilization process could be insufficient for insuring the level of sterility requested by the European Pharmacopea (one device with a residual contamination for one million of devices after the sterilization process). An increased time of processing, due to an unusual initial contamination could mean more damage to the shell, an insufficient time of sterilization could mean the eventual presence of a microorganism able to grow slowly in the prosthesis after implantation. The literature survey does not give information about the microflora able to grow in such silicones and the result of sterility control after explantation.

A last issue related to the ethylene oxide sterilization process should be considered. There is a possibility of leakage of residual ethylene oxide from a medical device after ethylene oxide sterilization. In this respect also sterilized PIP silicone breast implants need to be evaluated for conformity with current standards with regard to the level of residual ethylene oxide (EN ISO 10993-7:2008 Biological evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals, EN ISO 10993-7:2008/Cor 1:2009). In case of the presence of excess residual ethylene oxide, inflammation could be induced depending on the level and duration of the contact.

6.5.3 Risk from explantation

Risk of explantation can be subgrouped into risk associated with the anaesthesia and risk of complications from the breast surgery.

Regarding risk from anaesthesia it must be taken into consideration that:

- The overall majority of both cosmetic and reconstructive patients are healthy with no or little comorbidity.
- They have all undergone general anaesthesia to have the implants inserted, so they constitute a selected cohort with respect to that. In subsequent surgeries it is therefore possible with greater precision to judge the individual risk during anaesthesia and surgery.

In modern anaesthesia there is very low risk of death and serious complications, and in daily clinical life both patients and surgeons opt for general anaesthesia in case of complications (for instance capsular contracture) which renders the cosmetic result not satisfactory. This indicates that it is not a matter of great concern neither to patients nor to their physicians.

Regarding risk entailed with the breast surgery, there is always risk of immediate complications: infection and hematoma and delayed complications, the most important being: capsular contracture, malposition, pain, and rupture. The risks of immediate complications are low and rarely a contraindication. The risk of more delayed complications increase in revision surgery as compared with the primary surgery, however, not to an unacceptable level (FDA 2011). The indication for revision surgery should always be balanced with the potential risks of complications and this should be discussed with the patient. For healthy individuals it has been estimated that the risk of death is 1 in 250.000 anaesthesias Lienhart *et al.*, 2006). Anaesthesia may be complicated with aspiration or anaphylaxia. Generally, these risks are in the area of 1 in 6000 – 7000 cases, but lower for healthy persons (Fasting 2010).

Assessment of the risk in different sitations

a) *For explantation in the absence of rupture vs. in the case of rupture*?

Explanting an intact implant is a straight-forward procedure, takes about an hour for bilateral implants and the patient can usually go home the same day or the day after. In cases where the fibrous capsule needs to be removed, the procedure takes a little longer and there is more bleeding both during the procedure and afterwards. The patient is often treated with a drain which can produce secretion for several days. The pain and discomfort for the patient is probably slightly more in case of more extensive dissection, but in-hospital stay not necessarily longer, since patients can be sent home with drain.

b) *For explantation of smooth vs. textured vs. microtextured implants*?

In many cases there is no difference in explanting a smooth versus a textured implant, since many textured implants do not adhere to the surrounding tissue (microtextured and many textured implants). In cases with high-profile texturing/ large pores in the implant surface there is often in-growth of the capsular tissue into the texturing, but not always. It adheres like glue. In most cases the adherence can be loosened manually or blunt preparation. There are cases where sharp dissection is necessary, which will cause

slightly more bleeding and take more time. Exchange of smooth implants can be performed in local anaesthesia if no other procedures are going to take place and if the implant is intact. However, most surgeons and patients prefer general anaesthesia in any case.

c) *For explantation in the absence of inflammation vs. in the case of inflammation? (I imagine, no difference regarding the implant. But, what about the removal of lymph nodes?)*

If the tissue surrounding the breast implant is marked by inflammation, it is oedematous (containing tissue fluid), swollen and with lots of new tiny blood vessels. The tissue bleeds very easily and can be easy to damage and difficult to repair, sutures may for instance cut through and be difficult to place. If lymph nodes in the axilla are inflamed, painful and swollen it may be best to remove them. This is generally done by a separate incision in the axilla, but more incisions may be needed depending on the localisation of lymph nodes/granulomas to be removed. Any kind of lymph node dissection entails the risk of permanent problems with chronic seroma (accumulation of fluid), nerve damage and in cases of more extensive dissection a risk of lymph oedema – "swollen arm". The need for lymph node removal is not normally included in information to potential breast implantation patients.

d) *What are the benefits or avoided risks of explantation?*

The benefits of advising for elective (planned) explanting are: controlled circumstances where surgery can be planned within the patient's schedule, easier surgery in case on intact implant, presumably lower risk of complications with the new implant than if a rupture was present. Much lower risk of spilling of free silicone within the tissue, and shorter operation time in case of intact implant. In addition, if the non-medical grade silicone used in some or perhaps PIP silicone breast implants can cause local irritation it would be advisable to remove the implant before problems and symptoms occur rather than after.

e) *When rupture has occurred vs. when rupture has not occurred.*

In case of rupture of normal breast implants most surgeons advocate removal of the implant. Most patients also seek implant exchange in case of rupture. Several scientific studies indicate that many women have lived for a long period with ruptured implants without knowledge hereof and without occurrence of serious health problems (Hölmich *et al.*, 2001, Brown *et al.*, 2000). However, more local complications, in specific capsular contracture have been found. There is general consensus that implant rupture is rarely an emergency situation. In case of rupture of a PIP implant it seems sound to advice removal of the implant. The non-medical grade silicone gel may cause more tissue reaction than medical grade silicone which often do not cause any reaction. In such cases it would be advised to remove the fibrous capsule surrounding the ruptured implant along with the implant, both to avoid spillage of free silicone into surrounding tissues but also the clear the patient the most from the free non-medical grade silicone.

f) *When inflammation has occurred vs. when inflammation has not occurred.*

Inflammation is a reversible reaction, but can progress to fibrosis if the irritant persists/cannot be removed completely. Avoidance of inflammation is indeed preferable. Inflammation can be found by microscopy and may not always be clinically relevant, if the changes are minor. In case of clinical symptoms of inflammation (pain and swollen tissue), the microscopic changes are generally marked. If the patient has symptoms of inflammation there is a need to remove the implant as well as the surrounding fibrous capsule. Lymph nodes with marked inflammation and pain should also be removed and the patient should be followed regularly to identify potential progression and need for additional surgery. If the inflammation includes breast tissue, muscle on the chest or skin it may be necessary to excise these structures, which can impair both function as well as the cosmetic result heavily. In case of silicone spread to the axilla along facial planes as can be seen for instance after an accident it can be necessary to remove silicone from

the nerves in the brachial plexus. This situation is fortunately very rare. In case of local irritation from such silicone the long-term complications due to advancing fibrosis can be devastating.

g) *When lymph nodes have significantly swollen vs. have incurred the benign swelling generally associate with all silicon breast implants.*

Many women with silicone breast implants have lymph nodes in the axilla containing silicone. This is often due to migration of short chained silicone oils. In case of implant rupture also longer chained particles can be taken up in the regional lymph nodes. Normally such lymph nodes are not painful, only enlarged. But in case of inflammation, this is often accompanied by pain. There is no scientific evidence that containment of medial grade silicone within asymptomatic lymph nodes possesses any health threat. Enlarged lymph nodes may cause both patients and clinicians concern, however, the diagnosis is easily made by ultrasonography and in equivocal cases a fine needle aspiration. Lymph nodes in implant patients are normally only removed if they cause significant pain and distress, and this is rare.

7. OVERALL CONCLUSIONS ON THE RISKS AND BENEFITS FROM PIP AND OTHER BREAST IMPLANTS

7.1 General considerations

Regardless of manufacturer, a number of silicone breast implants will fail at some point after implantation. The risk factors for failure may be identified, namely:

a) The implant procedure. It has been shown in different studies that implant damage at insertion can weaken the implant and probably be responsible, at least in part for a later rupture. Electron microscopy scanning studies of failed implants have shown various types of failure mechanisms, from scalpel, scissor, needle and forceps lesions to abraded, weakened areas, probably caused by surgeons' fingers when they are stuffing an implant into its pocket. There is an estimation that a substantial proportion of the procedures in aesthetic breast surgery are carried out by non-specialists It is not clear whether this lack of suitable training is a major influence on subsequent breast implant failure rates

b) Time since the implantation. Breast implants can fail, regardless of manufacturer, and the probability of failure increases with time since implantation. This phenomenon is true for all types of implants used in the human body. Differences in diagnostic criteria and implant time in situ might account for large discrepancies in the reported number of ruptures in different clinical studies.

c) Physical and chemical features of the implant. Most implants comprise a single envelope. Besides breast implants a variety of medical devices are manufactured composed of silicone elastomers. The quality and purity of the silicone elastomer along with the effectiveness of the control over the chemical reaction for generating the gel can have a marked influence over the physical and chemical properties of a breast implant. The implants may on occasion have small, difficult to detect pinhole defects. Defects such as tiny cracks are sometimes also found where the posterior patch is 'welded' to the remaining implant.

d) Patient specific factors. There are two considerations, patient factors that may influence the integrity of the implant and factors that may influence the effects of leaked components. Apart from possible impacts of accidents rather little has been published on the influence of life style factors on breast implant integrity. The primary factors influencing patient vulnerability to leaked implant contents are also rather poorly researched.

7.2 Assessment of PIP silicone breast implants

There is no evidence that women who have had PIP silicone breast implants differ significantly initially in health status from those having implants from other manufacturers.

Important difficulties in making an assessment of the risks from PIP silicone breast implants are:

- In some countries and in some women, it is quite uncertain whether PIP silicone breast implants were used until explantation has been carried out.
- Reporting of breast implant failure and of any adverse effects on health due to this is not obligatory and consequently reported incident rates are frequently unreliable.

The SCENHIR is aware that PIP silicone breast implants have been found to vary considerably in composition and as a result are likely to vary substantially in performance characteristics. No clear temporal trend of implant problems has been identified for PIP silicone breast implants. Consequently it is very difficult to identify a truly representative PIP implant for risk assessment purposes.

The data available on PIP silicone breast implants is inevitably limited at this stage. The focus of attention in this initial response is on the following aspects:

- Physical and chemical properties of the PIP silicone breast implants, where available;
- Findings of the effects of PIP implant contents in the required animal tests, where available;
- Reports of incidents of PIP implant failures, where available.

Physical and chemical properties. The more recent PIP silicone breast implants, in common with those of other manufacturers, comprise a single envelope/shell. The implants consist of an outer shell filled with a gel. In common with those of most other manufacturers, they were manufactured using the polymer polydimethylsiloxane, also known as silicone. The chemical reaction resulting in crossed linked gel formation must be controlled because it governs the degree of crosslinking. The more variable the reaction, the greater the variation of the content of volatile and/or low molecular mass components in the implant (gel and shell). Use of industrial grade silicone along with a lesser control of the cross linking process appears to be associated with a higher content of low molecular weight components. As a consequence of the migration of these components it is reasonable to conclude that the shell might be weakened and that components could leak into the surrounding tissue. Tests conducted by the French Authorities on the physical integrity of a sample of PIP silicone breast implants indicated weaknesses in PIP shells not found in other commercially available implant.

Findings in Toxicity tests. A range of assays can be selected. For implant devices with prolonged contact the most extensive toxicity testing is indicated including cytotoxicity, sensitization, irritation, acute and subchronic systemic toxicity, genotoxicity, and implantation tests. Additional tests may be indicated by the risk assessment that is performed of a certain medical device/constituent such as biodegradation and toxicokinetic studies, chronic toxicity, carcinogenicity, immunotoxicity, neurotoxicity and reproductive/developmental toxicity. To date few studies aimed at evaluating the toxicity of the contents of PIP silicone breast implants have been conducted using tests specified for assessing the safety of Class III medical devices. The tests that were performed are designed to assess cytotoxicity, irritancy and genotoxicity. Medical grade silicone gels give negative results in these tests. In the case of the contents of the PIP silicone breast implants, tests for cytotoxicity and genotoxicity were negative. However, an *in vivo* test for irritancy was positive. This indicates the potential for inducing local irritancy when the silicone gel is released form the implant. The extent will depend on the amount released and local conditions. The implications of this positive result for irritancy, for women with PIP silicone breast implants, is currently uncertain and requires further investigation.

Incident reports. There are various methods to identify implant failure**.** It is important to note that clinical breast examinations alone have little sensitivity for detecting implant rupture. If there are also clinical signs of adverse effects, then a follow-up is likely to take place but a clinical examination is likely to miss implant rupture in the absence of positive signs. There is international agreement among professional radiologists and reconstructive and aesthetic surgeons that Magnetic Resonance Imaging (MRI) is by far the most accurate modality. Ultrasonography is the second best imaging modality for detecting implant rupture, but it is less precise and more operator dependent. Mammography is less useful.

There are cases reported suggesting that PIP silicone breast implants may have a higher failure rate in the first few years after implantation compared with those from other breast implant manufacturers. There are also a few case reports that ruptured PIP silicone breast implants may be associated with a higher incidence of swollen and painful lymph nodes.

The limited and selective clinical data and the absence of epidemiologic data on PIP silicone breast implants provide insufficient evidence to warrant a conclusion that women with PIP silicone breast implants have a greater risk to their health than women with

breast implants from other manufacturers. However, when the limited available information is taken together with the findings from tests of the physical and chemical properties of the shell and silicone and of the *in vivo* irritancy test, the possibility of health effects cannot be ruled out.

7.3 Generic Risks and Benefits of removal of PIP silicone breast implants

From a public health perspective it is important to identify generic risks and benefits. Such an assessment may not necessarily apply to an individual patient however.

As noted above there are obvious difficulties in providing scientifically based generic advice because:

- Over time, regardless of the manufacturer there will be an increased failure rate of the implants
- For many women it is uncertain whether their breast implant is a PIP manufactured implant
- Simple clinical examination alone is unlikely to identify those patients with a leaking/ruptured implant.
- Many such implants have been inserted by surgeons who are not qualified in plastic surgery. This might be a source of higher failure rates among their patients.

It is important to identify as far as possible high risk categories of patients based on the identified risk factors noted above. Manufacturers, duration of implant, patient symptoms and psychological state have been identified. However these criteria are insufficiently established at present and a patient by patient approach is therefore required. It is important that the risks identified in this opinion are considered in the light of the risks involved in prophylactic explantation.

7.4 Recommendations for further work

The SCENIHR recommends that further work is undertaken as a priority to establish with greater certainty the type and magnitude of health risks, if they exist, associated with PIP silicone breast implants.

In particular, the SCENIHR identifies the need for

(i) Chemical analysis: A thorough assessment of the composition of a range of PIP explants;

(ii) Assessment of biological effects: Further assessment of biological effects of the silicone gel used in PIP silicone breast implants/explants;

(iii) Simple tests: Simple tests that can be used for routine reliable low cost screening;

(iv) Data reporting procedures: The establishment of reliable data reporting procedures for silicone breast implants and nationwide data bases on SBI failures and other implant failures and the health effects of such failures. This should be a joint undertaking involving national governments, implant manufacturers and plastic surgeons;

(v) Research on explants to identify cause of failure: The FDA guidance document for saline, silicone gel, and alternative breast implants (FDA Nov. 2006) recommends the protocol developed by Brandon, *et al.* (2003a) for testing and analyzing explants. The FDA emphasizes detailed mechanical testing, scanning electron microscopy analysis (SEM), detailed chemical analysis, and comparison with a control group of unimplanted devices. It is recommended that this protocol be established as the "International Protocol for Testing and

Analyzing Explants and Controls." A standardized protocol would allow different laboratories throughout the world to compare their data.

A retrieval and analysis study of PIP explants and controls should be established using this protocol. The mechanical tests should include tensile strength, elongation, force-to-break, moduli, and tear resistance. The SEM examination should include an analysis of shell failure sites to determine the cause of failure and an overall characterization of explant and shell surfaces, emphasizing regions of shell degradation. Chemical analysis would involve extracting the non-crosslinked, low molecular weight silicones from the shell in order to determine the percent swelling. The extract should be analyzed to identify the low molecular weight silicone constituents in the shell. In addition platinum levels should be measured in the shell and the gel. Considering the various types of PIP silicone breast implants that have been manufactured, explants should be tested to determine if one particular type of PIP implant is failing or if failure is attributed to all types.

There are several types of diagnostic techniques available to analyze ruptured implants for failure mechanisms. Visual inspection, physical examination, and photographic analysis provide an overall description of the implant shape and gross features of the shell failure region. These techniques allow categorization and documentation of the mode of failure and are quite useful as a supplemental tool in the diagnosis of implant failure mechanisms. Microscopy techniques provide details of the ruptured shell region and can be used to determine the cause of breast implant failure. The use of field emission scanning electron microscopy (SEM) provides the state-of-the-art technique in the analysis of ruptured breast implants. Retrieval and analysis studies have used scanning electron microscopy to describe the morphology of several types of breast implant failures.

(vi) Improved testing protocols: The testing procedures and standards for breast implants should be refined to consider the interaction of the shell material with the filling gel and the surrounding body fluids, with respect to fatigue and tear resistance behaviour of the shell and the total implant.

8. OPINION

Mandate

To determine whether implanted PIP breast implants could give reasons for concern from the health point of view when compared with state of the art implants, taking into account their structure, composition and detected defects (*e.g.* low quality silicon, single envelop instead of double envelop) and the risk of rupture and oozing they may present;

General response

The data available presently on PIP silicone breast implants is necessarily limited at this stage, as the PIP manufacturer did no clinincal or epidemiologic research. So, the evidence on failure rates and complications related to PIP silicone breast implants are based on case reports. The large number of breast implant studies conducted to date and reported in the literature did not for the most part examine data by manufacturer. The focus of attention in this initial response is on the following aspects:

- Physical and chemical properties of the PIP silicone breast implants, where available;
- Findings of the effects of PIP implant contents in the required animal tests, where available;
- Reports of incidents of PIP implant failures, where available.

Physical and chemical properties: The more recent PIP silicone breast implants, in common with those of other manufacturers, comprise a single envelope/shell. The implants consist of an outer shell filled with a gel. In common with those of most other manufacturers, they were manufactured using the polymer polydimethylsiloxane, also known as silicone. The chemical reaction resulting in gel formation must be controlled because it governs the degree of crosslinking. The more variable this reaction is, the greater the variation of the content of volatile and/or low molecular mass components in the implant (gel and shell) is likely to be. Use of industrial grade silicone along with a lesser control of the cross linking process appears to be associated with a higher content of low molecular weight components. As a consequence of the migration of these components it is reasonable to conclude that the shell might be weakened and that components could leak into the surrounding tissue. Tests conducted by the French Authorities on the physical integrity of a sample of PIP silicone breast implants indicated weaknesses in PIP shells not found in other commercially available implant.

Findings in Toxicity tests: To date few studies aimed at evaluating the toxicity of the contents of PIP silicone implants sofar have been conducted using tests specified for assessing the safety of Class III medical devices. The tests that were performed are designed to assess cytotoxicity, irritancy and genotoxicity. Medical grade silicone gels give negative results in these tests. In the case of the contents of the PIP silicone implants, tests for cytotoxicity and genotoxicity were negative. However, an *in vivo* test for irritancy was positive. This indicates the potential for inducing local irritancy when the silicone gel is released form the implant. The extent will depend on the amount released, the duration of exposure and other local conditions. The implications of this positive result for irritancy for women with PIP silicone implants are currently uncertain and require further investigation.

Incident reports: There are cases reported suggesting that PIP silicone breast implants may have a higher failure rate in the first few years after implantation compared with those from other breast implant manufacturers. There are also a few case reports that ruptured PIP silicone implants may be associated with a higher incidence of swollen and painful lymph nodes.

The limited and selective clinical data and the absence of epidemiologic data on PIP silicone breast implants provide insufficient evidence to warrant a conclusion that women with PIP silicone breast implants have a greater risk to their health than women with breast implants from other manufacturers. However, studies among women with

standard-quality implants (including patient with ruptured implants) have shown that the risks of cancer and connective tissue disease are not increased among women with such implants. The limited available information, allied with the findings from tests of the physical and chemical properties of the shell and silicone and of the *in vivo* irritancy test, raises some concerns about the safety of PIP silicone breast implants as the possibility of health effects cannot be ruled out.

The SCENIHR is asked to identify the generic risks and benefits of various actions that might be taken to address these concerns. As noted above there are obvious difficulties in providing scientifically based advice because:

- Over time, regardless of the manufacturer there will be an increased failure rate of the implants;
- For many women it is uncertain whether their breast implant is a PIP manufactured implant;
- Simple clinical examination alone is unlikely to identify those patients with a leaking/ruptured implant;
- Many such implants have been inserted by surgeons who are not qualified in plastic surgery. This might be a source of higher failure rates among their patients.

It is important to identify as far as possible high risk categories of patients based on the identified risk factors noted above. Manufacturer, duration of implant,, patient symptoms and psychological state have been identified. However these criteria are insufficiently established at present and a patient by patient approach is therefore required. It is important that the risks identified in this opinion are considered in the light of the risks involved in unnecessary explantation.

Question 1A: What is the global reported incident rate associated with PIP breast implants;

Currently available data do not allow a reliable estimate.

Question 1B: How does this compare with the global reported incident rate for other breast implants;

Currently available data do not allow a reliable estimate.

Question 1C: What percentage of this global reported incident rate is associated with rupture of PIP breast implants?

Currently available data do not allow a reliable estimate.

Question 1D: What percentage of this global reported incident rate for PIP implants is associated with other adverse effects on health and what are these adverse health effects?

Currently available data do not allow a reliable estimate.

Question 1E: Is there evidence that PIP breast implants are more difficult to explant, before or after rupture, in comparison with other breast implants;

The evidence although limited indicates that there is no difference provided the device and fibrous capsule is intact. If the device has ruptured and particularly if it has caused substantial inflammation then the removal is more difficult. Thus a higher rupture rate of an implant made by a particular manufacturer would be problematic.

Question 1F: Is there evidence of any increased report of lymph node complications associated with the PIP breast implants?

There is evidence from an animal study of increase in irritancy. In contrast medical grade silicone gel does not cause detectable irritation in animal models. There is limited case history data in PIP explant patients indicating a possible increase in lymph node swelling and painful lymph nodes. It should be noted, however, that there may be overreporting of such conditions. This may arise due to reporting and ascertainment biases as a consequence of the widespread concern generated by media reporting on PIP silicone breast implants when compared to reporting of these conditions in non-PIP implant patients.

Question2

In case reasons for concern related to implanted PIP breast implants are identified, to make a risk/benefit analysis of explantation.

The evidence to date, indicating a health risk for women with PIP silicone breast implants, is not strong. However there is some concern regarding an increased inflammation from ruptured PIP silicone breast implants. It is not possible to make a general risk benefit statement at this time. Rather, for the time being, the risk benefit assessment needs to be based on a patient by patient basis by the aesthetic surgeon, bearing in mind the time since the implantation and the psychological state of the patient.

9. MINORITY OPINION

None.

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CASE REPORT

Cutaneous manifestation of silicone dissemination from a PIP implant - a case for prophylactic explantation?

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KEYWORDS
PIP;
Silicone;
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Summary The recent withdrawal of PIP (Poly Implant Prosthese, France) implants for breast augmentation enforced by the Medicines and Healthcare products Regulatory Agency (MHRA) on 31st March 2010 has ignited speculation into possible side effects relating to an unauthorized gel fill content. Local and migratory silicone granulomata and regional lymphadenopathy are well reported in the literature. Gel bleed from high cohesive gel implants with similar effect is also well known. However dissemination to sites distant from the breast manifest as cutaneous abnormalities in a patient implanted with a PIP product raises concern. We report such a case.

The recent withdrawal of PIP (Poly Implant Prosthese, France) implants for breast augmentation enforced by the Medicines and Healthcare products Regulatory Agency (MHRA) on 31st March 2010 has ignited speculation into possible side effects relating to an unauthorized gel fill content. This followed advice from Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS), the French regulatory authority resulting from their investigation of PIP implant manufacture prompted by reports of unacceptable rates of premature implant rupture.[1,2] The concern is shared by both patients and surgeons and reminiscent of experiences with Trilucent breast implants.

Local and migratory silicone granulomata and regional lymphadenopathy are well reported in the literature[3,4] particularly following former practice of using liquid silicone as a filler in breast augmentation and in the head and neck. Gel bleed from high cohesive gel implants with similar effect is also well known. Late complications following insertion of a PIP Hydrogel® breast implant have also been reported with the product recalled from the UK market in December 2000.[5] However dissemination to sites distant from the breast manifest as cutaneous abnormalities in a patient implanted with a PIP product raises concern. We report such a case.

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A 30-year-old female underwent bilateral breast augmentation for breast hypoplasia with PIP implants in 2005. She presented 5 years later with a 4-week history of progressive swelling of the left breast associated with pain that also involved the axilla. Examination revealed tense enlargement of the left breast with tender and marked axillary lymphadenopathy. Urgent ultrasound-guided aspiration was carried out which did not suggest rupture of the implant and which yielded approximately 200 ml of yellowish turbid fluid. Cultures of the aspirate failed to grow any organisms. Following aspiration the affected breast was much softer and more symmetrical in size compared with the contralateral side, but only briefly. Swelling of the breast recurred within hours and was followed a few days later by the development of new skin lesions appearing as small reddish papules in the left antecubital fossa (X2; see Figure 1), on the dorsum of the left hand (X1) and on the left thigh (X1) and right forearm (X1); the patient had no previous history of similar lesions and there was no obvious explanation for their presence.

The patient was subsequently admitted for bilateral capsulectomy and implant exchange replacing the old implants with standard silicone gel implants manufactured by Nagor Ltd. The capsule was found to be grossly thickened (approximately 5 mm) and floridly inflamed bilaterally; capsulectomy was extremely difficult to perform and was carried out piecemeal. On the left side there was a large volume, yellow-colored turbid effusion. Both implants appeared to have intact capsules but exhibited surface stickiness suggestive of silicone leakage. Due to significant hemorrhage and concerns about damage to the chest wall in particular, it was only possible to perform a complete anterior capsulectomy and a limited posterior capsulectomy. A single papule was also biopsied from the left antecubital fossa and sent for histological analysis along with a sample of capsule.

The patient made an uneventful immediate postoperative recovery and was discharged with arrangements for outpatient review. Review after 2 weeks revealed that the breasts had remained soft and there was no change in the appearance of the skin lesions that had erupted. Further review after 3 months once again revealed that the breasts were soft and symmetrical but there was substantial improvement in the appearance of the papular skin lesions evidenced by flattening and reduced erythema.

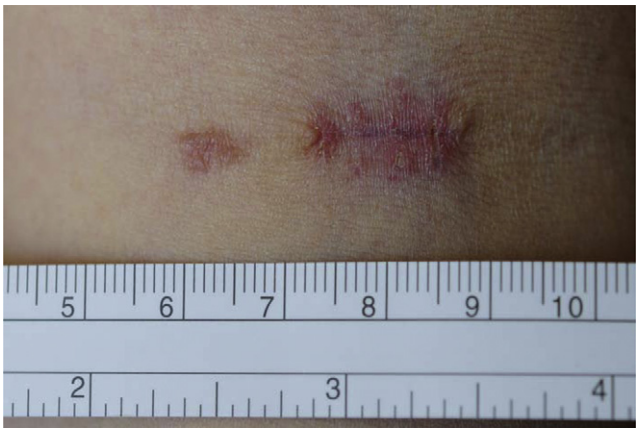

Figure 1 Skin lesions left antecubital fossa; only the lateral lesion has been biopsied as evidenced by the scar.

Microbiological analysis revealed no cells, organisms or growth. Histological analysis of the left capsule revealed florid non-caseating granulomatous inflammation surrounding clear spaces occupied by silicone (presumed) and biopsy of left antecubital skin showed dense non-caseating granulomatous inflammation throughout the dermis, including numerous multinucleate giant cells.

The clinical findings of breast enlargement due to effusion associated with tender lymphadenopathy can reasonably be explained by a leaking breast implant in this case. During surgery both breast capsules appeared grossly inflamed, which probably explains the rapid reaccumulation of effusion following aspiration. Histological features of granulomatous inflammation surrounding clear spaces consistent with particulate silicone in the capsular biopsies also suggest implant leakage. The presence of papular skin lesions on the limbs that bore similar histological features to the capsular specimens, albeit with absence of silicone particles, is strongly suggestive of migrating silicone granulomata.

MHRA analysis of PIP Hydrogel® breast implants did not support a recommendation for explantation unless clinically indicated. Similarly both UK and French studies show no evidence of toxicity or genotoxicity in PIP silicone implants to recommend explantation, a statement echoed and reinforced by BAPRAS. Safety concerns relating to cheap, low-quality breast implants evidenced by a propensity for premature rupture and with unapproved silicone gel fill persist but require further investigation.

Although PIP implants have now been appropriately recalled and quarantined it is possible that in future more patients will present with similar symptoms to those experienced in this case. Careful examination and selective biopsy of unusual skin lesions in such patients may be an indication for explantation if silicone granulomata are found.

Conflict of interest

None.

Funding

None.

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FDA Update on the Safety of Silicone Gel-Filled Breast Implants

June 2011

Center for Devices and Radiological Health
U.S. Food and Drug Administration

FDA Update on the Safety of Silicone Gel-Filled Breast Implants

Table of Contents

I. Introduction

Breast implants are medical devices that are used to augment breast size or to reconstruct the breast following mastectomy or to correct a congenital abnormality. Breast implants consist of a silicone outer shell and a filler (most commonly silicone gel or saline). Approximately 5 to10 million women worldwide have breast implants.

According to the American Society of Plastic Surgeons National Clearinghouse of Plastic Surgery Procedural Statistics, there were 296,203 breast augmentation procedures and 93,083 breast reconstruction procedures performed in the United States in 2010. Approximately half the procedures used saline-filled implants and half used silicone gel-filled implants. Figure 1 shows a photograph of woman holding a breast implant.

Figure 1. Photograph of a woman holding a breast implant.

II. Purpose

The FDA approved two silicone gel-filled breast implants in November 2006. This report provides an update on the clinical information about these products. The report includes:

- Preliminary data from the post-approval studies that the FDA required manufacturers to conduct as conditions of approval;
- A summary and analysis of adverse events reported to FDA since approval; and
- A review and analysis of recent clinical publications about the safety and effectiveness of silicone gel-filled breast implants.

This document is not intended to provide a comprehensive clinical update about the safety of saline-filled breast implants. Updated labeling and other information about saline-filled breast implants can be found on the FDA website at www.fda.gov/breastimplants.

III. Overview

History of the Regulation of Silicone Gel-Filled Breast Implants

Silicone gel-filled breast implants were introduced to the U.S. in 1962. When the U.S. Congress passed the 1976 Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act, breast implants were considered moderate risk (Class II) devices and required to comply with general controls and performance standards. The FDA reviewed new breast implants through the 510(k) premarket notification process as it did other Class II products.

In the early 1980s, concerns arose about the safety of breast implants, in particular silicone gel-filled breast implants. FDA's new surveillance systems identified frequent local complications and adverse outcomes, and other published case reports described cancer and connective tissue disease in some women with breast implants. In response, the FDA reclassified breast implant into Class III, higher-risk products needing premarket approval (PMA), and called for manufacturers to provide data demonstrating the devices were safe and effective.

In 1992, the FDA determined that the manufacturers had not adequately addressed public concerns about certain complications, such as implant rupture and silicone leakage. Following the advice of an outside expert advisory panel, the FDA removed all silicone gel-filled breast implants from the market and required manufacturers to submit premarket approval applications that contained data on safety and effectiveness.

In order to meet a public health need, the FDA allowed manufacturers to provide silicone gel-filled implants for reconstruction after mastectomy, correction of congenital deformities, or replacement of existing implants. Manufacturers enrolled women who received silicone gel-filled breast implants for these purposes in *Adjunct Studies* so that data could be collected about device performance and safety.

The FDA also called for more data on saline-filled breast implants, although it allowed them to remain on the market. During the next 14 years, with silicone gel-filled implants largely unavailable, many women opted for saline-filled breast implants.

In 1999, the Institute of Medicine (IOM) released a comprehensive report of the published literature and ongoing studies on breast implants, entitled *Safety of Silicone Breast Implants*.[1] The report made a clear distinction between local complications and systemic health concerns. It concluded that local complications were "the primary safety issue with silicone breast implants." These local complications, which included rupture, pain, capsular contracture, disfigurement, and serious infection, lead to medical interventions and repeat surgeries. Importantly, the IOM report concluded that there was no evidence that silicone breast implants caused systemic health effects such as cancer or autoimmune disease.

The FDA Breast Implant website, www.fda.gov/breastimplants contains a detailed Regulatory History of Breast Implants in the U.S.

U.S. Approved Silicone Gel-Filled Breast Implants

In November 2006, the FDA approved Allergan's* Natrelle Silicone Gel-Filled Breast Implants and Mentor's MemoryGel Silicone Gel-Filled Breast Implants. The FDA based its approvals on the manufacturers' clinical studies, called *Core Studies,* which followed hundreds of women with silicone gel-filled breast implants for 3 (Mentor) or 4 (Allergan) years. Despite frequent local complications and adverse outcomes, the FDA determined that the benefits and risks of breast implants were sufficiently well understood for women to make informed decisions about their use.

Data from each study are available in their respective PMA Summaries of Safety and Effectiveness. The FDA approved both devices for breast reconstruction for women of any age and breast augmentation for women at least age 22.

Postmarket Surveillance

When the FDA approved silicone gel-filled breast implants in the U.S. in 2006, it recognized that there were limited data on rare events and long-term outcomes. In order to better understand the long-term performance of these devices and to monitor for previously unrecognized adverse events, the FDA required the manufacturers to conduct post-approval studies, analyzed silicone gel-filled breast implant Medical Device Reports (MDR) submitted to FDA, performed periodic literature reviews, and evaluated correspondence from researchers, health care providers, patients, and concerned citizens.

Conditions of Approval

As conditions of approval, the FDA required each manufacturer of silicone gel-filled breast implants to conduct six post-approval studies to characterize the long-term performance and safety of the devices. The FDA believes that data from these long-term, post-approval studies will provide important information for women, their families and friends, and health care providers, and may lead to improvements in implant design and labeling.

Due to the length of the studies required by the FDA, they have not all been completed. Rather than waiting for all studies to be completed, FDA believes it is important to share currently available information so that women may make informed decisions about their health care.

The required post-approval studies for silicone gel-filled breast implants are as follows:

* Allergan was formally known as Inamed, which was formerly McGhan.

(1) *Core Post-Approval Studies (Core Studies)* – To assess long-term clinical performance of breast implants in women that enrolled in studies to support premarket approval applications. These studies were designed to follow women for 10 years after initial implantation.

(2) *Large Post-Approval Studies (Large Studies)* – To assess long-term outcomes and identify rare adverse events by enrolling more than 40,000 silicone gel-filled breast implant patients and following them for 10-years.

(3) *Device Failure Studies (Failure Studies)* – To further characterize the modes and causes of failure of explanted devices over a 10-year period.

(4) *Focus Group Studies* – To improve the format and content of the patient labeling.

(5) *Annual Physician Informed Decision Survey (Informed Decision Study)* – To monitor the process of how patient labeling is distributed to women considering silicone gel-filled breast implants.

(6) *Adjunct Studies* – To provide performance and safety information about silicone gel-filled breast implants provided to U.S. women from 1992-2006, prior to approval, when implants could only be used for reconstruction and replacement of existing implants.

IV. Detailed Summary of Post-Approval Studies for Silicone Gel-Filled Breast Implants

Key Points from Post-Approval Studies

The FDA required each company to design and conduct six post-approval studies as conditions of approval.

Key local complications and adverse outcomes observed include capsular contracture, reoperation, and implant removal. Other local complications include implant rupture, wrinkling, asymmetry, scarring, pain, and infection.

The local complications observed in the silicone gel-filled breast implant post-approval studies are consistent with complications noted at the time of approval.

The longer a woman has silicone gel-filled breast implants, the more likely she is to experience local complications or adverse outcomes. As many as 1 in 5 primary augmentation patients and 1 in 2 primary reconstruction patients require implant removal within 10 years of implantation.

Limitations in the post-approval studies to date preclude the detection of very rare rates of complications. However, post-approval studies to date do not show evidence that silicone gel-filled breast implants cause connective tissue disease or reproductive problems.

Differences in study design, clinical endpoints and definitions, and patient populations preclude direct comparisons of the post-approval study results for the two approved silicone gel-filled breast implants.

Patient follow-up rates are lower than anticipated, limiting the ability to draw definitive conclusions and to detect rare complications.

This represents an interim analysis of currently available data. Data collection is on-going.

NOTE: *This section contains detailed results from the post-approval studies of silicone gel-filled breast implants based on reports that the FDA received and validated as of May 31, 2011. Each manufacturer developed its own scientifically sound study design and statistical analyses. As a result, there are important differences between the two studies, including variations in number of study participants, patient enrollment criteria, clinical endpoints and definitions. These differences preclude direct comparisons of the two approved silicone gel-filled breast implants. In some cases, low patient follow-up rates may limit interpretation of the data.*

As conditions of approval, the FDA required Allergan and Mentor to conduct six post-approval studies, including: (1) *Core Studies*, (2) *Large Studies*, (3) *Device Failure Studies*, (4) *Focus Group Studies*, (5) *Annual Physician Informed Decision Studies*, and (6) *Adjunct Studies*.

For the *Large Study,* the FDA required each manufacturer to report interim study results twice each year for the first 2 years and annually thereafter. In addition, manufacturers provide quarterly updates on *Large Study* enrollment and follow-up. For all other studies, the manufacturers must submit annual reports to the FDA until study completion.

Both manufacturers have completed their *Focus Group Studies*. The other post-approval studies are ongoing. Both manufacturers have closed enrollment for their *Core Studies* and *Large Studies*. Follow-up in those studies continues but has been below target rates. Table 1 shows the enrollment and current follow-up status of each post-approval study.

Participants in the *Core Studies* and the *Large Studies* were enrolled in one of the following study cohorts:

Primary Augmentation – women who received breast implants to increase the size of their breasts.
Primary Reconstruction – women who received breast implants to replace breast tissue that was removed due to disease or trauma or that failed to develop properly.
Revision Augmentation – women who received breast implants to correct or improve the results of primary breast augmentation surgeries.
Revision Reconstruction – women who received breast implants to correct or improve the results of primary breast reconstruction surgeries.

Core Post-Approval Studies (*Core Studies)*

Purpose:
The purpose of the *Core Studies* was to gather data on longer-term safety and effectiveness of silicone gel-filled breast implants among participants enrolled in the studies conducted prior to approval, and to evaluate the effectiveness of magnetic resonance imaging (MRI) screening in detecting implant rupture.

Study Design:
The *Core Studies* followed participants enrolled in pre-approval studies of silicone gel-filled breast implants, and conducted clinical assessments of patients at six months, 1 year and annually thereafter for a total of 10 years.

Each study assigned participants to either an MRI group or a non-MRI group. Participants in the MRI group received MRIs on a specific schedule to screen for rupture. The timing of the MRI assessments and the methods of assigning participants to the MRI group differ by manufacturer. In addition, all participants (MRI group and non MRI group) received MRIs any time there were symptoms of a rupture.

The Allergan *Core Study* enrolled 715 patients and the Mentor *Core Study* enrolled 1,008 patients. Table 2 presents enrollment numbers for the *Core Studies* by indication, manufacturer, and MRI study group status.

Based on the 2010 annual reports, the preliminary follow-up rates at 10 years post-implant are 66 percent for Allergan, and at 8 years post-implant are 58 percent for Mentor (Table 1). Longer

term follow-up is available for the Allergan *Core Study* participants because the study began enrolling patients approximately 20 months before the Mentor *Core Study*.

Each study had some patients who were not available for follow-up because they had died or discontinued participation.

Final results should be available in 2012, after all patients have been followed for at least 10 years.

Results:

Local Complications and Adverse Outcomes

The most frequently observed complications and adverse outcomes in each *Core Study* include capsular contracture, reoperation, removal of the implant, and implant rupture. Other common complications cited in the Allergan study included asymmetry, scarring, and breast pain. Other common complications cited in the Mentor study included changes in nipple and breast sensation. Cumulative incidence rates of complications are displayed in Table 3 (Allergan) and Table 4 (Mentor).

Several observations can be made based on the available data. First, not surprisingly, the cumulative incidence rate of each complication increases over time.

Second, complication rates vary greatly depending on the type of surgery performed (primary vs. revision, augmentation vs. reconstruction). For many of the complications and adverse outcomes, rates are higher for patients undergoing revision augmentation and primary reconstruction than for primary augmentation. For example, the incidence of breast implant removal by 10 years post-implant for patients receiving Allergan silicone gel-filled breast implants is 32.4 percent for revision augmentation patients and 53.8 percent for primary reconstruction patients compared to 20.8 percent for primary augmentation patients. Similarly, for Mentor patients at 8 years post-implant, the incidence of breast implant removal is 21.1 percent for revision augmentation patients and 23.3 percent for primary reconstruction patients compared to 7.3 percent for primary augmentation. Detailed cumulative incidence rates of capsular contracture, reoperation, and implant removal are displayed in Table 5 and Table 6.

Third, the longer women had breast implants, the more likely they were to have them removed. In the *Core Studies*, Allergan reported a total of 293 implant removals over 10 years of follow-up, and Mentor reported a total of 195 implant removals over 8 years of follow-up. The most frequent reasons for implant removal for each study were capsular contracture, rupture, malposition, and wrinkling or ripping. Table 7 and Table 8 present data on the reasons for implant removal.

Finally, the most frequently reported reason for reoperation varied with type of surgery. A reoperation is defined as any additional surgical procedure performed on the breast and/or implant after initial breast implantation and includes minor surgical procedures such as breast biopsies.

In the *Core Studies*, Allergan reported 434 reoperations on 285 patients over 10 years, and

Mentor reported 385 reoperations on 276 patients over 8 years post-implant. The majority of silicone gel-filled breast implant patients in the *Core Studies* did not require reoperation.

For both manufacturers, capsular contracture and breast asymmetry were the most common reasons for reoperation in the primary augmentation and primary reconstruction groups, respectively. Other significant reasons for reoperation included the need for biopsy, breast cancer mass, implant malposition, breast sagging (ptosis), implant rupture, hematoma or seroma, scarring, and patient request for style or size change. Table 9 and Table 10 show details of the reasons for reoperations for each manufacturer.

Rupture Rates

In each *Core Study*, rupture rates varied by device and indication. The cumulative incidence of rupture rates among Allergan implants in the MRI group at 10 years post-implantation (95 percent confidence intervals) were as follows:

Primary augmentation	10.1 percent (7.4 to 13.7)
Revision augmentation	6.3 percent (2.8 to 13.7)
Primary reconstruction	27.2 percent (17.3 to 41.3)
Revision reconstruction	6.7 percent (0.2 to 31.9)

The cumulative incidence of rupture rates among Mentor implants at 8 years post-implantation (95 percent confidence intervals) were as follows:

Primary augmentation	13.6 percent (7.6 to 23.6)
Revision augmentation	15.5 percent (6.5 to 34.6)
Primary reconstruction	14.0 percent (7.6 to 25)
Revision reconstruction	21.3 percent (7.3 to 53.3)

In the Allergan *Core Study*, the majority of ruptures were accompanied by symptoms; depending on the cohort, up to 35 percent of ruptures may be silent.

Connective Tissue Diseases (CTD)

Among the Allergan *Core Study* participants, over 10 years of follow-up, there have been nine diagnoses of CTD. These include four cases of rheumatoid arthritis, three cases of fibromyalgia, one case of Raynaud's Syndrome, and one case of undifferentiated CTD.

Among the Mentor *Core Study* participants, over the 8- year period of follow-up, there have been 28 confirmed diagnoses of connective tissue, autoimmune, or rheumatic disease in 21 patients. These include seven reports of fibromyalgia, six cases of rheumatoid or inflammatory arthritis, three cases of chronic fatigue syndrome, three cases of thyroid-related disease, one case of systemic lupus erythematosis, and eight other miscellaneous and unspecified CTD cases.

Reproduction and Lactation Problems
In the *Core Study*, Allergan reported 45 post-implant reproduction problems in 44 patients over 10 years; most of the problems were spontaneous abortions, miscarriages or infertility. Most of the problems occurred in the primary augmentation and revision augmentation groups. In Allergan's primary reconstruction group, there was one report of a planned abortion to treat a medical problem and one report of no menses. There were no reports of post-implant reproduction problems among women who received the implants for revision reconstruction.

In Allergan's primary and revision augmentation groups, there were 30 post-implant problems with lactation reported in 24 patients, predominantly inadequate milk production. No post-implant lactation problems were reported among women who received the implants for reconstruction or revision reconstruction.

In the *Core Study*, Mentor reported 153 patients with pregnancies over 8 years. Twenty-three of these patients reported miscarriages, and one patient reported a stillborn delivery. Seventy patients reported attempting to breastfeed and of these, 13 reported lactation difficulties and nine reported an inadequate milk supply.

Breast Cancer
In the Allergan *Core Study,* 602 patients received silicone gel-filled breast implants for primary or revision augmentation. Of these, five were diagnosed with breast cancer through 10 years of post-implant follow-up.

In the Mentor *Core Study,* there were four new diagnoses of breast cancer among the 697 primary and revision augmentation patients through 8 years of follow-up.

Discussion:
The long-term follow-up of participants in the *Core Studies* demonstrates that a significant percentage of women who receive silicone gel-filled breast implants experience complications and adverse outcomes.

The most frequently observed complications and adverse outcomes include capsular contracture, reoperation, removal of the implant, and implant rupture. The cumulative incidence of these complications increases over time – the longer a woman has breast implants, the more likely she is to experience a complication.

These studies did not demonstrate an association of silicone gel-filled breast implants with CTD, reproductive or lactation problems, or breast cancer. However, it is important to note that these studies were not designed to estimate the incidence of rare disease outcomes, nor were they designed to compare silicone gel-filled breast implants to alternative therapies.

Large Post-Approval Studies (*Large Studies*)

Purpose:

The purpose of the *Large Studies* is to determine the incidence of complications and other adverse outcomes, including local complications, connective tissue disease, neurological disease, potential effects on offspring of women with breast implants, potential effects on reproduction and lactation, cancer, suicide, rupture, potential interference of breast implants with mammography, and patient compliance with recommendations for MRI follow-up.

The studies were designed to be large enough to address issues that the *Core Studies* were not powered to answer, as well as to provide a real-world assessment of some outcomes of silicone gel-filled breast implantation surgery.

Study Design:

Both Allergan and Mentor are in the midst of these 10-year, multi-center, prospective follow-up studies in women who received silicone gel-filled breast implants after FDA approval in 2006. Each study includes a control group of women who received saline-filled breast implants during the same time period.

In each of the *Large Studies*, participants are followed annually for 10 years. Data are collected using patient questionnaires (completed online, via mail, or telephone) and clinical follow-up visits (conducted three to four times during the course of the study).

Allergan designed its *Large Study* with 39,390 women with silicone gel-filled breast implants and a control group of 19,605 women with saline-filled breast implants. In October 2008, at Allergan's request, the FDA approved a reduction in the control group sample size to 15,240, based on FDA's calculation that this number of participants would be sufficient to meet the study objectives.

Allergan initiated patient enrollment in the *Large Study* in February 2007 and closed enrollment in March 2010, with a total of 41,342 silicone gel-filled breast implant recipients and 15,646 saline breast implant recipients. The results reported here are taken from Allergan's 2010 annual report. They include data for all participants with 2 years of follow-up.

Mentor's designed its *Large Study* with 41,900 women with silicone gel-filled breast implants and a control group of 1,000 women with saline-filled breast implants. Mentor initiated patient enrollment in the *Large Study* in February 2007, and closed enrollment in July 2009, with a total of 41,975 silicone gel-filled breast implant participants and 1,030 saline breast implant participants. The results reported here are taken from Mentor's 2010 annual report. They include data for all participants with 3 years of follow-up.

Among *Large Study* participants, 97 women enrolled in the Allergan study and 556 women enrolled in the Mentor study were under age 22, which did not meet the enrollment criteria. The tables and analyses of Allergan's data contained in this report include these patients. The tables and analyses of Mentor's data include only the 41,419 patients who met the original enrollment criteria. The FDA has asked Mentor to provide data and analyses on these younger women in future analyses.

Table 11 and Table 12 summarize the number of participants enrolled in Allergan's and Mentor's *Large Studies* by implant type and indication as reported in the 2010 study interim reports. In each company's *Large Study,* the majority of participants received implants for primary augmentation, with revision augmentation, primary reconstruction, and revision reconstruction occurring in decreasing frequency.

Results:

Baseline Social and Demographic Characteristics

Participants in Allergan's *Large Study* had a median age of 35, height of 5'5" and weight of 130 pounds. The majority of subjects were Caucasian (68.6 percent). Most attended or graduated from college (72.1 percent), were married (51.8 percent), and had professional occupations (45.2 percent). At baseline more than half of the participants (57 percent) had never smoked. More than two thirds of the current smokers (67.5 percent) reported smoking 10 or fewer cigarettes per day. The majority of subjects (63.3 percent) consumed no more than three alcoholic drinks per week, and 19.5 percent did not drink at all.

Among participants of known age in Mentor's *Large Study,* 78.2 percent of the silicone gel-filled breast implant participants and 49.8 percent of the saline breast implant participants were at least 30 years old. Among Mentor's participants in the primary augmentation group of known age, 70.4 percent of the silicone gel-filled breast implant recipients and 47.5 percent of the saline breast implant recipients were at least 30 years old. Silicone gel-filled breast implant participants had a median height of 5'5'' and median weight of 130 pounds. Saline breast implant participants had a median height of 5'3'' and median weight of 129 pounds.

Most participants in Mentor's *Large Study* attended or graduated from college (75.6 percent of silicone gel-filled breast implant recipients and 63.9 percent saline breast implant participants) and were married (59.5 percent silicone gel-filled breast implant recipients and 44.2 percent saline-filled breast implant recipients). For silicone gel-filled breast implant participants, 44.4 percent had ever smoked regularly and 70.7 percent were current alcohol drinkers. For saline breast implant participants, 38 percent had ever smoked regularly and 61.1 percent were current alcohol drinkers.

The FDA asked both manufacturers to closely monitor and report the racial/ethnic distribution of participants during the enrollment period to ensure participation that appropriately represented the demographics of the U.S.

The racial distribution of the Allergan *Large Study* participants at baseline was 71 percent Caucasian, 13 percent Hispanic, five percent Asian, three percent Black/African American and three percent other. There were six percent of participants for whom racial/ethnic information was unavailable.

In the Mentor *Large Study*, the racial/ethnic distribution of the Mentor MemoryGel silicone gel-filled implant recipients was 77.8 percent Caucasian/not of Hispanic origin, 9.9 percent Caucasian of Hispanic origin, 4.5 percent Asian, 2.2 percent Black not of Hispanic origin, 0.4 percent Black of Hispanic origin, 0.7 percent Native America/Alaska Native, 2.5 percent other,

and 2.1 percent unknown or not provided. Among the saline implant group in the Mentor study the race/ethnicity distribution was 56.5 percent Caucasian/not of Hispanic origin, 26.5 percent Caucasian of Hispanic origin, 7.7 percent Asian, 2.8 percent Black not of Hispanic origin, 1.2 percent Black of Hispanic origin, 0.9 percent Native America/Alaska Native, 4.6 percent other. Of note, for participants in the primary augmentation cohort of Mentor's study, for whom race/ethnicity was known, 76.7 percent of the MemoryGel participants and 54.7 percent of the saline participants were Caucasian, not of Hispanic origin.

Follow-Up

Follow-up rates reported to the FDA in the 2010 *Large Study* progress reports fell below targets. In addition, because not all women enrolled in the studies at the same time, follow-up duration varies. In some cases, these factors may limit interpretation of the data.

Allergan *Large Study* follow-up rates are 60.5 percent and 45.1 percent for silicone gel-filled breast implant participants and saline breast implant participants, respectively, 2 years after implantation. Follow-up rates for silicone gel-filled breast implant participants by indication are:

Primary augmentation	53 percent
Revision augmentation	55 percent
Primary reconstruction	75 percent
Revision reconstruction	69 percent

For the Mentor, *Large Study*, follow-up rates 3 years after implantation are 21.1 percent and 9.6 percent for silicone gel-filled breast implant participants and saline breast implant participants, respectively. The follow-up rates for silicone gel-filled breast implant participants by indication are:

Primary augmentation	20 percent
Revision augmentation	19 percent
Primary reconstruction	29 percent
Revision reconstruction	28 percent

Operative Techniques and Implant Characteristics

In the Allergan *Large Study,* 95.9 percent of participants received bilateral implants. Incision sites were most commonly inframammary (54 percent) and periareolar (22.8 percent). Most devices were placed either in a partial (58.9 percent) or complete (29.3 percent) submuscular position. The vast majority of implants had smooth surfaces (91.3 percent). In this study, the most commonly used implant size in both the silicone and saline cohorts was 300-399 cc (42.4 percent). The most common incision sizes were 4- 4.99 cm (32.5 percent) for silicone gel-filled

implants and 3-3.99 cm (43.2 percent) for saline implants, which reflect the fact that saline implants are filled after placement so the incision size can be smaller.

In the Mentor *Large Study,* 95.1 percent of silicone participants and 98.6 percent of saline control participants received bilateral implants. In the primary augmentation cohort, the inframammary surgical approach was used for 58.6 percent of the implants and 26.9 percent of the saline-filled implants. For silicone gel-filled and saline-filled participants, mastectomy scar was the most common surgical approach in the primary reconstruction cohort (72.8 percent and 57.9 percent respectively). The most common placement of the devices was submuscular for all cohorts in both treatment groups.

Local Complications and Adverse Outcomes
Allergan reports the 2-year cumulative incidence of local complications and other adverse outcomes as follows:

a. Reoperation. 6.5 percent for silicone gel-filled breast implant participants and 4.5 percent for saline breast implant participants.

b. Rupture. 0.5 percent for silicone gel-filled breast implant participants and 2.5 percent for saline breast implant participants (saline implant deflation).

c. Capsular Contracture (Grades III/IV). 5.0 percent for silicone gel-filled breast implant participants and 2.8 percent for saline breast implant participants.

d. Implant removal with or without replacement. 3.4 percent for silicone gel-filled breast implant participants and 2.4 percent for saline breast implant participants.

Mentor reports the 3-year cumulative incidence of local complications and other adverse outcomes for silicone gel-filled breast implant recipients as follows:

a. Reoperation. 10.8 percent for augmentation, 14.6 percent for revision-augmentation, 20.4 percent for reconstruction, 17.7 percent for revision-reconstruction.

b. Rupture. 0.2 percent for augmentation, 1.0 percent for revision-augmentation, 0.4 percent for reconstruction, 0.7 percent for revision-reconstruction.

c. Capsular Contracture (Grades III/IV). 5.3 percent for augmentation, 11.8 percent for revision-augmentation, 9.1 percent for reconstruction, 10.0 percent for revision-reconstruction.

d. Implant removal with or without replacement. 5.0 percent for augmentation, 7.7 percent for revision-augmentation, 13.5 percent for reconstruction, 11.7 percent for revision-reconstruction.

The *Large Studies* are collecting information on reasons for implant removal. In the Allergan study, the three most frequent reasons for device removal were desire to change size/style,

capsular contracture, and implant malposition. In the Mentor study, the three most frequent reasons for device removal were size change at patient request, infection, and asymmetry. Table 13 and Table 14 provide details of the reasons for device removals.

Rare Outcomes
In the Allergan *Large Study*, forty-three (0.6 percent) silicone gel-filled breast implant participants and 14 (0.4 percent) saline breast implant participants had new reports of CTD at 2 years follow-up. In the silicone gel-filled breast implant group, nine women reported fibromyalgia, four reported rheumatoid arthritis, nine reported fibromyalgia, three reported systemic lupus erythematosus, and 27 reported miscellaneous, undifferentiated, unspecified or "other" CTDs.

At 2 years follow-up, 80 silicone gel-filled breast implant subjects (1.2 percent) have reported a diagnosis of any cancer post-implantation. There were 18 silicone gel-filled breast implant participants with neurological disorders (0.3 percent) at year 2.

In the Mentor *Large Study*, the incidence rates per 10,000 person-years for CTD at 3 years follow-up were: 27.2 for rheumatoid arthritis (83 new cases), 70.9 for osteoarthritis (210 new cases), 3.9 for scleroderma (12 new cases), 4.2 for systemic lupus erythematosus (13 new cases), 5.9 for Sjögren's Syndrome (18 new cases), 22.4 for other connective tissue diseases (68 new cases), and 26.4 for fibromyalgia (80 new cases).

The incidence rates per 10,000 person-years for newly diagnosed cancer at 3 years follow-up were: 59.7 for all types of cancer (136 new cases), 13.6 for breast cancer (31 new cases), 0.9 for lung cancer (2 new cases), 0.0 for brain cancer, and 45.2 for other cancers (103 new cases). The incidence rate per 10,000 person-years for new neurological disease at 3-years was 36.0 for all types (111 new cases).

Discussion:
Reoperation, implant removal, rupture, capsular contracture, and other complications and adverse outcomes affect a significant proportion of women receiving silicone gel-filled breast implants. To date, the results of the *Large Studies* have not identified any previously unrecognized health concerns nor do they suggest a causal link between silicone gel-filled breast implants and CTD or breast cancer.

Data interpretation is limited due to low follow-up rates and the on-going nature of the study. The FDA has actively worked with the manufacturers to identify methods to improve the rate of study follow-up and to encourage patients and physicians to continue their participation in these studies.

Allergan conducted focus groups to better understand how patients may be motivated to complete follow-up visits and the annual questionnaire. Most respondents agreed that reminder e-mails, mailings, and telephone outreach would encourage them to continue participation.

Based on that feedback, Allergan launched a revised website for their *Large Study* that allows participants to complete the required questionnaire online. New options include personalized

pages, the ability to complete the questionnaire by phone, and the ability to update personal contact information online. In addition, Allergan issued a new direct-to-participant mailer. After these efforts, the annual number of complete questionnaires doubled.

To address their low *Large Study* follow-up rates, Mentor requested that the FDA write letters to patients and physicians. The FDA and Mentor sent more than 40,000 letters to study physicians and patients—these letters are available on the FDA Post-Approval Studies webpage. The letters encouraged ongoing patient participation and stressed the importance of continued follow up through study completion.

In response to these letters, Mentor and the FDA received significant feedback from study participants. Reasons cited by patients for failure to follow-up included geographical relocation, voluntary study discontinuation, and difficulty accessing the study website. The Mentor patient study webpage has since been modified at FDA's request.

Notably, *Large Study* follow-up rates vary by indication and appear consistent with findings identified in the *Core Studies*. Higher follow-up rates are observed among reconstruction participants, possibly because of their increased access to medical care for on-going monitoring of their underlying medical condition. It appears that once augmentation patients have received their implants and recovered from their surgery, they are less inclined to continue study participation than reconstruction patients.

Device Failure Studies (*Failure Studies*)

Purpose:

The purpose of these studies is to evaluate silicone gel-filled breast implants that have been retrieved and returned to Allergan and Mentor, and to document and catalog the failure modes in order to improve implant design and surgical techniques. Not all returned implants were removed because of local complications or rupture.

Each manufacturer was required to conduct studies of all retrieved devices returned to them until both the *Core Study* and the *Large Study* are completed. The data collection and analysis vary by manufacturer.

These studies are designed to: (1) further evaluate breast implant failures inadvertently caused during implantation, (2) characterize surgical instrument damage to breast implants, (3) evaluate and characterize failures that occur due to localized breast implant shell stress, and (4) determine if surgical factors (e.g., incision size) predispose to device rupture.

Allergan Results:

Since the beginning of its post-approval studies through June 30, 2009, 2,674 devices were returned to and analyzed by Allergan. Nine of these implants were excluded from the summary due to damage that occurred during shipping.

Allergan evaluated 2,665 devices in the laboratory with the following results:

87 (3.3 percent) devices could not be analyzed
1,429 (53.6 percent) devices were found to be "Intact and Functional," with no openings or other failure characteristics;
158 (5.9 percent) had "Gel Related Observations," with defects related to gel-related characteristics without loss of shell integrity.
91 (3.4 percent) had "Device Surface Observations," with defects related to the size or appearance of the device but not associated with an opening or deformation of the device.
900 (33.8 percent) had openings in the shell. Of the devices with openings:
51 (1.9 percent) devices had fold flaws,
26 devices (1 percent) had manufacturing defects,
487 (18.3 percent) had surgical damage or surgical impact, and
336 (12.6 percent) devices had openings for which the cause could not be identified.

Mentor Results:

Among patients participating in the Mentor *Large* post-approval study, 62 silicone gel-filled breast implants were retrieved; 35 (56.5 percent) were intact or without abnormality, and 27 (43.5 percent) had openings. Among the implants with openings, Mentor reported that 12 were damaged by sharp instruments and 15 had openings of unknown cause.

Among *Core Study* participants, 97 devices were explanted and returned to Mentor for evaluation from August 2000 to August 2009. Seventy-three of the 97 devices (75 percent) were returned intact and without abnormality. Of the 24 devices that ruptured, eight were damaged by sharp instruments, two had partial delamination in the shell or patch juncture, and 14 had a rent of unknown cause.

Discussion:

The most common cause of rupture reported in the device retrieval studies is damage to the implant during the implantation surgery. However, only a small proportion of breast implants are returned to the manufacturers for evaluation. This limits the ability to identify trends in failure modes.

Focus Group Study

Purpose:

The FDA required both manufacturers to complete *Focus Group Studies* to improve the format and content of the labeling. Both manufacturers completed their *Focus Group Studies* in 2007.

Allergan Focus Group Study:

Allergan's *Focus Study* had six focus groups, each of which had up to 10 participants, 18 years of age and older who had a breast implant or were considering breast implants. There were 29 augmentation breast implant participants and 23 reconstruction breast implant participants.

Based on its *Focus Group Study,* Allergan reorganized and modified its product labeling to include implant photos, graphs depicting change in cup size for augmentation, and additional information about patient satisfaction, quality of life, and long-term complications.

Mentor Focus Group Study:
There were four focus groups in Mentor's *Focus Group Study,* each of which had eight to 10 participants. Thirty-five adult women interested in silicone gel-filled breast implants for augmentation or reconstruction participated. Participants completed a self-administered survey designed to collect individual data and to measure their comprehension of information from Mentor's educational brochure. Respondents in both the augmentation and reconstruction groups agreed that the brochure was highly informative and comprehensive. Many respondents felt they learned new information as a result of reading the brochure. Based on the feedback from the focus groups, Mentor modified its brochure to more clearly outline differences between restoration, replacement, reconstruction, and revision and to provide information to help women weigh the risks and complications with the benefits of breast implants.

Annual Physician Informed Decision Survey (*Informed Decision Study*)

Purpose:
The FDA required both manufacturers to institute a formal informed decision process to ensure that: (1) a woman has obtained the patient information brochure with adequate time to read it prior to surgery, and (2) the surgeon has documented that the patient has an adequate understanding of the risks and follow-up recommendations associated with the device.

The FDA also required the manufacturers to provide physician training in the use of their informed decision process as part of physician training program for the implants. In addition, the FDA required each manufacturer to conduct a survey using a new random sample of 50 physicians each year to assess the patient informed consent process.

Results:
Based on the 2009 surveys for each manufacturer, physicians found the patients' brochures informative, useful, and effective in communicating breast implant risks and benefits. However, not all physicians use the brochure. For example, Allergan's survey showed that only 52 percent of physicians provide the brochure as part of the surgery consultation process.

Adjunct Studies

Purpose:
In 1992, when FDA removed all silicone gel-filled breast implants from the market, the FDA continued to permit companies to provide these devices for reconstruction after mastectomy, correction of congenital deformities, or replacement of existing implants. Women who received silicone gel-filled breast implants for these purposes were enrolled in *Adjunct Studies* so that data about device performance and safety could be collected. Participant enrollment began in 1992 for Mentor and 1997 for Allergan.

As a condition of approval of silicone gel-filled breast implants in 2006, both manufacturers were required to close enrollment of new patients into the *Adjunct Studies* but continue to follow study participants through their 5-year post-implant evaluations.

Allergan enrolled 83,968 women in its *Adjunct Studies*, including 44,799 who underwent primary reconstruction and 39,169 who underwent breast implant revision. The revision group included women who underwent both revision augmentation and revision reconstruction. Patients had a median age of 42 years (range, 14 to 98).

Mentor enrolled 136,609 women in its *Adjunct Studies*. Reconstruction surgery was performed in 57,828, revision reconstruction surgery in 18,491, and revision augmentation in 60,290 women.

Results:
The 5-year rates for the most common local complications and adverse outcomes observed in the Allergan *Adjunct Study* for patients undergoing primary reconstruction and revision, respectively, were capsular contracture (Baker III/IV) (16.3 percent, 22.6 percent), asymmetry (11.9 percent, 11.3 percent), implant palpability/visibility (7.7 percent, 12.2 percent), and wrinkling (6.2 percent, 9.4 percent).

For Mentor, the most common local complications and adverse outcomes in the primary reconstruction, revision reconstruction, and revision augmentation groups, respectively, were asymmetry (23.1 percent, 11.1 percent, 25.8 percent), wrinkling (13.4 percent, 14 percent, 17.4 percent), and explant (10.7 percent, 9.9 percent, 12.8 percent). Other reported additional procedures included nipple reconstruction, reconstruction revision/staged reconstruction, and capsulectomy. The most common reasons for removal were capsular contracture, infection, patient request for size and implant change, and leakage/rupture/deflation.

Discussion:
The *Adjunct Studies* provide qualitative information about the spectrum of adverse outcomes that occur in this patient population. However, data collection methodology and low follow-up rates (23 percent for Allergan and 16 percent for Mentor 5 years post-implant) limit data interpretation.

Post-Approval Study Conclusions

Overall, the post-approval studies conducted to meet the six conditions of approval demonstrate that the longer a woman has silicone gel-filled breast implants, the more likely she is to experience complications or adverse outcomes. The most common local complications and adverse outcomes associated with silicone gel-filled breast implants include capsular contracture, reoperation, and implant removal. Other local complications include implant rupture, wrinkling, asymmetry, scarring, pain and infection. Actual complication rates vary according to the reason for breast implantation.

These observations are consistent with complications and adverse outcomes previously known to

be associated with breast implants.

The post-approval studies to date do not show evidence that silicone gel-filled breast implants cause CTD, reproductive problems, or breast cancer. Low follow-up rates and other study limitations may limit interpretation of the data and preclude the detection of very rare complications.

Both manufacturers have encountered challenges in implementation of their study protocols, and follow-up rates are lower than expected. As follow-up has lagged, the FDA recognizes that these studies may not provide the data necessary to definitively answer questions about rare associations. The FDA has been working with manufacturers to address challenges related to enrollment and follow-up rates. See FDA Activities for more details.

For more information about breast implant post-approval studies, please visit the FDA Post-Approval Studies webpage.

V. Postmarket surveillance of adverse events reported on approved silicone gel-filled breast implants

Key Points from Postmarket Surveillance of Adverse Events

The primary goals of FDA's postmarket medical device surveillance are to identify previously unrecognized adverse events and to help to detect patterns of actual or potential adverse events.

Allergan and Mentor must submit adverse event reports on silicone gel-filled breast implants received after November 2006 through one of two reporting methods:

- Medical Device Reports (MDR), or
- Postmarket Spreadsheet Reports (PSR).

Patients and healthcare providers can also submit adverse event reports directly to FDA through MedWatch, FDA's safety information and adverse event reporting program.

Overall, the types of adverse events submitted to the FDA are consistent with results from premarket and post-approval studies. No unexpected outcomes or complications were reported through December 2010, except for rare reports of possible Anaplastic Large Cell Lymphoma (ALCL) associated with breast implants. For additional information on breast implants and ALCL see: Anaplastic Large Cell Lymphoma (ALCL) in Women with Breast Implants: Preliminary FDA Findings and Analyses.

Background:
The FDA collects and analyzes adverse event information from a variety of sources as part of its ongoing surveillance of silicone gel-filled breast implants.

Manufacturers and user facilities (such as hospitals and nursing homes) are required to submit device-related reportable events according the Medical Device Reporting (MDR) regulation (21 CFR Part 803). User facilities are required to report device-related deaths to FDA and device-related deaths and serious injuries to the manufacturer.

Allergan and Mentor must submit adverse event reports for patients who received silicone gel-filled breast implants through one of two reporting methods:

1) Medical Device Reports (MDR). Manufacturers must report all deaths and unusual, unique or uncommon adverse events to FDA as individual reports on the FDA Form 3500A within 30 days of becoming aware of the event, or

2) Postmarket Spreadsheet Reports (PSR). Manufacturers must report serious injuries and malfunctions that are well-known or expected to occur based on data from the premarket clinical trials in PSR reports. PSR reports are submitted quarterly, as authorized under 21

CFR Part 803.19(c), as an alternative to the requirement for submitting individual MDR reports on FDA Form 3500A.

Health care professionals, patients and other concerned individuals who do not have a mandatory reporting obligation, can submit reports voluntarily to the FDA through MedWatch, FDA's safety information and adverse event reporting program.

Individual reports submitted by breast implant manufacturers and user facilities are stored in FDA's Manufacturer and User Facility Device Experience (MAUDE) database, a repository for adverse event reports involving medical devices. Voluntary reports from health care professionals and patients are also stored in the MAUDE database. PSR reports are not included in the MAUDE database.

Postmarket Spreadsheet Reporting (PSR):
The FDA designed the PSR program specifically to monitor the postmarket performance of approved silicone gel-filled breast implants. The PSR program, an alternative to the requirement for submitting individual MDR reports, requires manufacturers to submit quarterly reports for serious injuries and malfunctions that are well-known or expected to occur based on data from the premarket clinical trials (e.g., rupture, capsular contracture).

The PSR program requires manufacturers to collect more specific and more detailed information about these well-known adverse events than would normally be submitted on an individual reporting form. The additional details include the patient's race/ethnicity, whether the patient is enrolled in the *Large Study*, the reason for implanting the device, whether a reoperation (with or without implant removal) was performed as a result of the adverse event, the reason for reoperation, the reason for implant removal, whether the removed implant was replaced and if so, with what type of implant, and the type of surgery performed. Collection of these data will help characterize the known breast implant-related problems and improve data analysis.

Reports from the MDR and PSR reporting systems are described in Tables 15 - 18. The data are grouped according to assigned patient problem codes and device problem codes. Patient and device problem codes are provided by the FDA for use by the manufacturer when submitting an adverse event report. (For more information about codes see Event Problem Codes).

Results of Postmarket Surveillance of Adverse Events:
Patient and Device Problems Submitted to the FDA as Individual MDRs
Between November 17, 2006 (date of FDA approval) and December 31, 2010, the FDA received 133 individual MDRs associated with Allergan and Mentor silicone gel-filled breast implants. Manufacturers submitted 24 of these reports, user facilities submitted 25 reports, and voluntary reports accounted for 84.

The types of events associated with these reports are two deaths, 84 serious injuries, 21 malfunctions, eight "data element is blank" and 18 "other" (a type of event used by the reporter when the adverse event is not considered a death, injury or malfunction report).

The two death reports referred to the same patient who was diagnosed with anaplastic large cell

lymphoma (ALCL). This patient's pathology report later confirmed that she had systemic ALCL, not ALCL localized to her breast implants. For more information about ALCL and breast implants see: Anaplastic Large Cell Lymphoma (ALCL) in Women with Breast Implants: Preliminary FDA Findings and Analyses.

The 133 reports contained a total of 530 patient problem codes and 239 device problem codes. Table 15 and Table16 list patient problems and device problems that occurred in more than 1 percent of the MDR reports.

Patient and Device Problems Submitted to the FDA through the Postmarket Spreadsheet Reporting (PSR) System
Between November 17, 2006 and December 31, 2010, the FDA received 16,681 reports through the PSR: 16,279 reports of injuries and 402 reports of implant malfunctions. A total of 26,511 patient problems were reported in 16,681 PSR reports.

The most frequent patient adverse events and outcomes reported were reoperations (noted by the code 'surgical procedure'), capsular contracture, pain, infection and breast lumps. The primary reasons for reoperations were rupture, capsular contracture, implant malposition/asymmetry, infection, wrinkling and hematoma. The primary reasons for implant removal were implant rupture, capsular contracture, malposition/asymmetry, infection, wrinkling and extrusion.

A total of 12,327 device problem codes were reported in 16,681 PSR reports. The most frequently reported device problems were device-patient incompatibility, rupture, implant malposition/asymmetry, and device defects that prevented the surgeon from implanting the device (includes codes for 'tears, rips, holes in device,' 'device material that prevented the device from being implanted,' 'design/structure problems,' and 'out of the box failures'). The term 'device-patient incompatibility' is a code used to indicate a biological reaction that the patient has to the implant.

Table 17 and Table 18 list patient problems and device problems that occurred in more than 1 percent of the PSR reports.

Discussion of Adverse Event Data:
There are strengths and limitations to the data collected through FDA's adverse event reporting systems. Strengths of the system include the ability to detect rare or unexpected device-related adverse events, the capacity to identify problems in the real world setting (unlike premarket trials) and collection of information about problems that occur over a long period of device use.

Because the number of patient and device problems reported to the FDA is subject to underreporting, MAUDE and PSR data are not intended to be used either to evaluate rates of adverse events or to compare adverse event occurrence rates across devices.

Specifically, the MAUDE and PSR data are subject to a number of limitations, including:

- The number of events that are reported to the FDA is often much lower than the number of events that actually occur. Whether an event is reported may be influenced

by the severity of the adverse event, how unusual it is or whether there has been a lot of publicity or legal action involving the product.

It is generally not possible to independently verify the reports received by the FDA. As a result, they may contain incomplete or inaccurate information. The FDA assumes that reports received are truthful.

The size of the population exposed to the device (denominator) is often not known, so it is difficult to determine adverse event rates and put the number of adverse events in perspective to interpret the data.

It is difficult to know whether or not the implant caused or contributed to the adverse event based solely on information provided in a report. Establishing a cause and effect relationship is especially difficult if the device is not examined or if the analysis was inadequate.

In summary, the results collected to date through the adverse event reporting system are consistent with the results obtained from the premarket and post-approval studies. With the exception of ALCL occurring in association with breast implants, no new complications or adverse outcomes associated with breast implantation have been identified.

VI. Review of the Literature on the Safety of Silicone Gel-Filled Breast Implants

Key Points from Literature Review

This section reviews the epidemiologic literature published in peer-reviewed journals since 2005 on the clinical safety and effectiveness of silicone gel-filled breast implants. It focuses on outcomes that have not been addressed to date in post-approval studies.

Most women report high levels of satisfaction with their body image and the shape, feel and size of their implants.

Most infections develop in the immediate post-operative period, although infections can develop long after implant. Late infection may be underreported.

The current body of literature does not support an association between CTD and silicone gel-filled breast implants, but most of the available studies have limitations.

There is no evidence that suggests untoward effects of silicone gel-filled breast implants on pregnancy or fertility

Current evidence does not support an association between mothers with breast implants and difficulty with breast feeding or adverse health events in their children.

Women with breast implants may be more likely to be diagnosed with anaplastic large cell lymphoma (ALCL). See Anaplastic Large Cell Lymphoma (ALCL) In Women with Breast Implants: Preliminary FDA Findings and Analyses.

Although some studies show an increased risk of suicide in women with breast implants, this is likely due to selection bias. No study has demonstrated a causal relationship between breast implants and suicide.

Background:
At the time of their approval in November 2006, silicone gel-filled breast implants were associated with several well-characterized complications and adverse outcomes, including rupture, reoperation, and capsular contracture. Data concerning these results are presented in the Post-Approval Study (Section V) and Post-Market Surveillance of Adverse Event (Section VI) sections of this report and are not discussed here.

When the FDA approved Allergan and Mentor's silicone gel-filled breast implants in 2006, there were reports of other potential adverse events, but they were infrequent and not fully understood. These included implant-related infections, CTD, cancer, reproductive outcomes, and suicide. In addition, there were limited data on patient satisfaction. These results are discussed in this section.

This section summarizes medical and scientific English literature published primarily from January 1, 2005 through December 31, 2010. The literature search included reviews and meta-analyses of human studies, as well as selected original papers. If significant publications concerning a particular adverse event of interest had not been published during the relevant time period, manuscripts from earlier time periods were evaluated.

Patient Satisfaction and Quality of Life:

Satisfaction of patient expectations remains an important measure of the effectiveness of cosmetic surgery. Patients undergoing breast augmentation surgery have reported high rates of satisfaction with the shape, feel, and size of their silicone gel-filled breast implants.[2-8]

Studies show that many women undergo breast augmentation surgery to improve their self-esteem and self-image.[2, 5] More than 90 percent of women with silicone gel-filled breast implants are satisfied that their primary expectations have been met. Body image improves in the majority of women who receive silicone gel-filled breast implants, and this satisfaction lasts for at least two years post-implant.

Post-operative complications such as capsular contracture decrease satisfaction with the procedure, particularly if those complications are visible to other people.[2]

Infections:

Estimates from scientific and medical literature on the risk of infection following silicone gel-filled breast implantation are derived mainly from prospective studies in Scandinavian countries.[9, 10] Wound infections occur in less than 5 percent of breast implant study participants. Along with hematoma, infections are the most common short-term local complication. Infections generally occur in the immediate period following surgery.[9] Systemic infections are not typical although toxic shock syndrome has been rarely reported.[11]

Acute infections associated with breast implants are generally linked to skin pathogens (i.e., group A streptococci, Staphylococcus epidermidis, or Staphylococcus aureus), while long-term infections are often caused by aerobic gram-negative bacilli. Chronic "culture-negative" infections after breast implant procedures are sometimes due to atypical mycobacteria. Although two-thirds of infections develop within the acute post-operative period, some infections may develop years or even decades after surgery. The reported rate of systemic and late infections is approximately 1 percent or less, although it is likely that late infections are under-reported.[12, 13]

Subclinical infection may predispose to long-term complication that follows breast implantation, i.e., capsular contraction that involves the formation and contraction of a collagenous sheath around the implant, thus forming hard, spherical masses in the breasts.

While systemic postoperative wound infections are rare, the effects can be devastating. Among the Mycobacteria, Mycobacterium fortuitum complex represent the opportunistic pathogens that account for 60 to 80 percent of postsurgical wound infections caused by rapidly growing mycobacteria, particularly after breast surgery (with or without prosthetic implants).[14-16] Complications include long term infection occurring months after implantation. Drainage or

implant removal is usually required to ensure bacterial eradication.[17]

Connective Tissue Diseases/Rheumatic Conditions:

Connective tissue diseases (CTDs) include a spectrum of conditions such as fibromyalgia, scleroderma, Sjögren's Syndrome, and systemic lupus erythematosus. A number of studies evaluated the possibility of a relationship between silicone gel-filled breast implants and connective tissues diseases.[18-37]

Estimate of CTD differ. For example, the incidence of fibromyalgia is approximately 1,128 women per 100,000 women in the general population according to one study.[38] Comparatively, the incidence of scleroderma in a general population is much lower, occurring in approximately 3 patients per 100,000 per year.[39]

Because of the incidence and prevalence[40] of CTDs are quite low,[38, 39] a very large study of sufficient duration would be required to determine a causal relationship between silicone gel-filled breast implants and CTD.

Most studies have not found an association between connective tissue diseases as a group and silicone gel-filled breast implants. The FDA collaborated on one study in 2001 that found a positive association between extracapsular silicone gel-filled breast implants and fibromyalgia, but significant study design and patient selection weaknesses undermine the study's conclusions.[41]

Most studies that have examined specific connective tissue diseases like fibromyalgia, scleroderma and systemic lupus erythematosus have failed to identify an association, although the studies have recognized limitations, such as lack of very long-term duration of follow-up.[25, 33, 37]

Overall, the current body of evidence does not support an association between silicone gel-filled breast implants and CTD.

Cancer:

Women who receive silicone gel-filled breast implants for augmentation do not appear to be at increased risk of developing breast cancer.[42, 43] In fact, studies suggest they may be at average or even lower risk – with some estimating a risk reduction of 10 to 50 percent.[44]

Survival rates for women with breast cancer who receive silicone gel-filled breast implants as part of breast reconstruction appear to be unaffected by the presence of an implant.[44]

Some reports have observed an increase in cancer risk for patients with cosmetic breast implants (not specifically silicone gel-filled breast implants), including brain, cervical, vulvar, lung, and non-melanoma skin cancer.[45] However, these observations appear unrelated to the effects of the implants themselves.[10, 46] Post-approval studies have not identified an increased cancer risk among silicone gel-filled breast implant recipients.

One possible exception is the rare development of Anaplastic Large Cell Lymphoma (ALCL) in

women with breast implants. Reports in the scientific community have suggested a possible association between ALK-negative ALCL and silicone gel-filled and saline-filled breast implants. In a thorough review of scientific literature published from January 1997 through May 2010, the FDA identified 34 unique cases of ALCL in women with breast implants throughout the world. The FDA's adverse event reporting systems also contain 17 reports of ALCL in women with breast implants. Additional cases have been identified through the FDA's contact with other regulatory authorities, scientific experts, and breast implant manufacturers. In total, the FDA is aware of approximately 60 case reports of ALCL in women with breast implants worldwide. For additional information, see Anaplastic Large Cell Lymphoma (ALCL) In Women with Breast Implants: Preliminary FDA Findings and Analyses.

Other than ALCL, the available epidemiologic evidence does not support a clinical association of silicone gel-filled breast implants with an increased cancer risk in humans. Results from several recent published large scale cohort studies with long-term follow-up provide no evidence of an association between breast implants and cancer.[42, 43, 47]

Screening for Breast Cancer:
Screening mammograms are X-ray images of the breast used to look for changes in the breast tissue that are too small to cause noticeable symptoms; in some cases these represent breast cancers.[48] Breast implants may make it difficult to see breast tissue on standard mammograms; additional X-ray images, called implant displacement views, can be obtained at the time of a mammogram and should be used to examine the breast tissue more completely in breast implant patients.[49]

The National Cancer Institute advises women with breast implants to receive screening mammography, at experienced centers, at intervals based on their age and risk factors. Women should be sure to notify the mammography facility and the technologist conducting the exam that they have breast implants.

The National Cancer Institute recommendations for breast cancer screening in women with breast implants can be found at http://www.cancer.gov/cancertopics/factsheet/Detection/mammograms.

Screening for Rupture:
When a silicone gel-filled implant ruptures, the gel may remain in the shell or in the scar tissue that forms around the implant (intracapsular rupture). In some cases, the silicone migrates outside of scar capsule (extracapsular rupture). It may be difficult or impossible to remove silicone gel that has migrated out of the capsule to other parts of the body.

Different diagnostic tests can be used to detect intracapsular and extracapsular breast implant rupture, including magnetic resonance imaging (MRI), mammography, ultrasound, and computed tomography (CT).

MRI can be used to detect both intracapsular and extracapsular ruptures. In the older models of silicone gel-filled breast implants, MRI can detect more than 90 percent of ruptures.[50]

A recent meta-analysis on the diagnostic accuracy of MRI for detecting silicone gel-filled breast implant ruptures reported lower accuracy in detecting ruptures in asymptomatic patients than in symptomatic patients.[51]

One of the post-approval studies required by the FDA looks at the accuracy of MRI in detecting rupture.

The FDA approved labeling for silicone gel-filled implants currently recommends that women get their first breast MRI 3 years after they receive the implants and every 2 years thereafter to detect silent ruptures.

MRIs are not an option, however, for women who have MRI incompatible pacemakers, aneurysm clips, or other implanted metallic foreign bodies, or whose physical size and weight precludes them from having an MRI.[50]

Once implants are removed, there is no medical need for routine screening MRI.

Mammograms can detect extracapsular silicone when an implant ruptures, but they do not detect intracapsular ruptures. In older models of silicone gel-filled breast implants, only 10 to 22 percent of ruptures are extracapsular, so mammograms will miss most ruptures.[50] If extracapsular silicone is detected by mammography, before making a presumptive diagnosis of implant rupture, the physician should take a careful clinical medical history from the patient to rule out the possibility that the silicone remains from a prior rupture or silicone injection (and thereby unrelated to the current silicone gel-filled breast implant).

The relative value of ultrasound alone to detect intracapsular ruptures is controversial because its accuracy depends on the skill of the ultrasound technologist, the type of equipment used, and the experience of the interpreting physician.[50] Ultrasound is limited in its ability to detect ruptures in the back wall of the implant and in the breast tissue behind it. Extracapsular silicone has a distinctive appearance on ultrasound and should be recognized if imaged. As with mammography, extracapsular silicone detected on ultrasound may be due to a previous implant rupture or silicone injection. Therefore, a thorough clinical history is important to make an accurate diagnosis.

CT scans can detect intracapsular silicone gel-filled breast implant rupture, but they are limited in their ability to detect extracapsular ruptures. This imaging technique is a useful alternative for women who are unable to have MRIs. However, a disadvantage of CT is that it exposes patients to ionizing radiation.[50]

Effects on Reproductive Outcomes:
There is no significant evidence that suggests untoward effects of silicone gel-filled breast implants on pregnancy or fertility.

The bulk of the published literature in the field of maternal and child health to date does not suggest a causal relationship between silicone gel-filled breast implants and adverse health outcomes in children born to women with implants.[10, 52] In addition, silicone gel-filled breast

implants do not appear to be associated with breastfeeding difficulties.[53, 54]

Suicide:
Retrospective studies consistently suggest an increased rate of suicide in patients undergoing breast implants compared to the general population. However, it is likely that this reflects underlying factors including socioeconomic status and self-esteem. There is no evidence that breast implants cause the observed increase in suicide risk.[55-58]

VII. Summary of Key Findings

1. Based on the totality of the evidence, the FDA believes that silicone gel-filled breast implants have a reasonable assurance of safety and effectiveness when used as labeled. Despite frequent local complications and adverse outcomes, the benefits and risks of breast implants are sufficiently well understood for women to make informed decisions about their use.

2. The longer a woman has breast implants, the more likely she is to experience local complications or adverse outcomes. Women with breast implants will need to monitor their breasts for local complications for the rest of their lives.

3. The most frequent complications and adverse outcomes experienced by breast implant patients include capsular contracture, reoperation, and implant removal (with or without replacement). Other frequent complications include implant rupture, wrinkling, asymmetry, scarring, pain, and infection, among others. These observations are consistent with the local complications and adverse outcomes that were known at the time of approval.

4. Women with breast implants may have a very small but increased likelihood of being diagnosed with anaplastic large cell lymphoma.

5. In the post-approval *Core Studies*, between 20 to 40 percent of augmentation patients and 40 to 70 percent of reconstruction patients had reoperations during the first 8 to 10 years after they received their implants. Although routine replacement is not necessary, many women will need additional surgery to modify, remove, or replace their implants.

6. There is no apparent association between silicone gel-filled breast implants and connective tissue disease, breast cancer, or reproductive problems. Associations that are very rare or that take many years to manifest may not be detected using currently available data.

7. MRI continues to be the most effective method of detecting silent (asymptomatic) rupture of silicone gel-filled breast implants.

8. Interpretation of the data from the silicone gel-filled breast implant post-approval studies may be limited by low follow-up rates.

VIII. Recommendations for Patients Who Have or Who Are Considering Breast Implants

Be aware that breast implants are associated with significant local complications, and the longer the devices remain implanted, the more likely you are to experience a complication. Local complications and adverse outcomes include capsular contracture, reoperation, removal, and implant rupture. Many women also experience breast pain, wrinkling, asymmetry, scarring, and infection.

Continue to receive routine follow-up with your physician. This includes having periodic MRI exams to detect "silent rupture" of the implant.

Notify your health care provider if you develop any unusual signs or symptoms including pain, asymmetry, hardness or swelling.

Recognize that breast implants are not lifetime devices. The longer you have your implants, the more likely it will be for you to have them removed.

If you have enrolled in an Allergan or Mentor post-approval study, continue to participate. These studies are the best way to collect information about the long-term rates of complications.

Continue routine screening mammography for breast cancer at intervals recommended by your health care provider based on your age and risk factors.

IX. Recommendations for Health Care Providers

- Provide women with copies of patient brochures and informed consent so that they have access to the critical information needed to make informed decisions about receiving and caring for breast implants. Labeling for Approved Breast Implants for patients and for physicians is available on FDA's breast implant website.

- Maintain medical vigilance through follow-up and post-approval studies so that the long-term effects of silicone gel-filled breast implants can be better understood. Your contributions provide data that are used to evaluate how new surgical techniques, patient characteristics, and implant characteristics influence the cosmetic and health outcomes of patients undergoing breast implantation.

- Screen for silent rupture using MRI. Women with silicone gel-filled breast implants should undergo MRI screening for silent implant ruptures at 3 years post-implantation, and every 2 years thereafter.

- Report breast implant associated adverse events and deaths to FDA via MedWatch.

X. FDA Activities

The FDA activities surrounding silicone gel-filled breast implants focus on three key goals:

Fostering the collection of data about implant performance;
Improving the follow-up rates in current and future post-approval studies; and
Communicating new safety information when it becomes available so that women can make informed decisions about their healthcare.

To accomplish these goals, the FDA:

Closely monitors the status and conduct of the on-going required post-approval studies so that data is collected, validated scientifically and disseminated widely;

Actively encourages and facilitates adverse event reporting by the manufacturers, patients, healthcare providers, and health care facilities;

Is collaborating with the American Society of Plastic Surgeons (ASPS) and other experts in the clinical and scientific community to develop a registry of women with breast implants and anaplastic large cell lymphoma (ALCL) to better understand the nature and possible factors contributing to their association;

Will hold a meeting of its Medical Device Advisory Committee in the summer of 2011 to seek input on issues related to postmarket surveillance of silicone breast implants including study design, patient enrollment and follow-up, and data analysis;

Released, in June 2011, a newly updated breast implant website (www.fda.gov/breastimplants). Key sections of this website describe the risks of breast implants, the questions women should ask their doctors before getting breast implants, and what women should expect during the surgical procedure and recovery.

Developed a new Breast Implants Complications Booklet for patients. The booklet includes the latest information from the post-approval studies. It is available on the FDA website.

Requires breast implant manufacturers to update their labeling each time the data is reanalyzed. The most current Labeling for Approved Breast Implants is available on the FDA website.

XI. Conclusion

Based on the totality of the evidence, the FDA believes that silicone gel-filled breast implants have a reasonable assurance of safety and effectiveness when used as labeled. Despite frequent local complications and adverse outcomes, the benefits and risks of breast implants are sufficiently well understood for women to make informed decisions about their use. Manufacturers and physicians should continue to provide balanced and up-to-date information to women considering breast implants to help inform their decisions.

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XIII. Glossary of Terms

Adverse Event Report: A report submitted to the FDA describing an undesired outcome for which a device association is known or suspected. Also known as a Medical Device Report (MDR).

Adjunct Studies: Specific to silicone gel-filled breast implants, these studies were originally designed by FDA to address the public health need for reconstruction and revision patients. By participating in these studies women and surgeons gained access to the silicone gel-filled breast implants not on the open market.

ALCL: Anaplastic Large Cell Lymphoma, a rare type of T-cell non-Hodgkin's lymphoma. ALCL is a rare type of non-Hodgkin's lymphoma. ALCL is not cancer of the breast tissue. Lymphoma is a cancer of the lymphatic cells of the immune system.

Asymmetry: Lack of proportion of shape, size, and/or position between the two breasts.

Augmentation: A surgical procedure to increase breast size. For this document, it refers to placement of a breast implant. The first time a breast implant is placed to increase breast size, it is called primary augmentation. All subsequent times the implant is replaced, it is called revision augmentation.

Capsular Contracture: A tightening of the fibrous capsule surrounding a breast implant, resulting in firmness or hardening of the breast. One of the most common complications of breast implant surgery.

Capsulectomy: The surgical removal of capsular contracture around the breast implant

Capsulorraphy: A surgical procedure to revise the shape and size of the pocket in which the breast implant lies.

Class III device: FDA uses a risk based model to assign devices into one of three classifications: Class I, II, or III. A Class III designation represents the highest risk profile. A Class III device requires premarket approval and a scientific review to ensure the device's safety and effectiveness, in addition to the general controls for lower risk devices.

Cohort: a group of study participants who share similar conditions, characteristics or demographics

Condition of Approval: Postmarket obligation defined by FDA that the manufacturer must comply with as part of the terms for receiving authorization to market a specific device.

Connective Tissue Disease (CTD): any disease that targets the connective tissues of the body; they may be heritable (such as fibromyalgia), autoimmune (such as rheumatoid arthritis) or other (such as scurvy).

Core Studies (specific to breast implants): Clinical studies on silicone gel-filled breast implants required of Mentor and Allergan after the FDA approved their devices in 2006. The purpose of these studies is to assess long-term clinical performance of breast implants in women that enrolled in studies to support premarket approval applications.

Epidemiologic Study: A statistical study on a human population that attempts to link health outcomes with a specific cause.

Extracapsular: Occurring outside the fibrous scar capsule surrounding the breast implant.

Federal Food, Drug, and Cosmetic Act: The law which gives FDA its regulatory authority.

Follow-up rates: the indication of how often the manufacturer maintains contact with the patient after the initial breast implant surgery in the collection of post-implant study data. The follow-up rate reflects the manufactures success in data collection.

Focus Group Studies: A form of quality research in which participants are gathered together and are asked about their perceptions, opinions, beliefs and attitudes towards a specific issue or item. Questions are asked in an interactive group setting where participants are free to talk with other group members.

Iatrogenic Injury/Damage: Injury or damage an implant resulting from a surgical procedure.

Institute of Medicine (IOM): The Institute of Medicine is a US not for profit governmental organization. Its purpose is to provide national advice on issues relating to biomedical science, medicine, and health, and its mission to serve as adviser to the nation to improve health. It works outside the framework of the U.S. federal government to provide independent guidance and analysis.

Intracapsular: Occurring inside the fibrous scar capsule surrounding the breast implant.

Lactation: the act of producing milk from the mammary glands in the breast.

Large Studies (specific to breast implants): Clinical studies on silicone gel-filled breast implants required of Mentor and Allergan after the FDA approved their devices in 2006. The purpose of these studies was to assess long-term outcomes and identify rare adverse events by enrolling more than 40,000 silicone gel-filled breast implant patients, following them for 10-years, and comparing them to control groups of saline-filled breast implant patients.

Mammography: An x-ray of the breast tissues

Meta-analysis: A combined evaluation of multiple similar studies

MRI (Magnetic Resonance Imaging): a diagnostic testing process that uses magnets and no ionizing radiation in creating images that provide clear contrast between soft and dense tissues. MRI provides a level of clarity that may not be obtainable by routine x-ray.

Post-Approval Studies: Studies conducted as conditions of approval after the device receives FDA authorization to begin marketing. Post-approval studies provide a means for data collection from a large population over an extended period of time.

Reconstruction: A surgical procedure to replace breast tissue that has been removed due to cancer or trauma or that has failed to develop properly due to a severe breast abnormality. The first time a breast implant is placed for reconstruction, it is called primary reconstruction. All subsequent times the implant is replaced, it is called revision reconstruction.

Reoperation: Any additional surgical procedure performed on the breast and/or implant after initial breast implantation.

Rupture: Specifically associated with silicone gel-filled breast implants, it represents the condition whereby there is a tear or hole in the implant's outer shell.

Saline-Filled Breast Implant: A device intended to be implanted in the breast area of the body to replace or supplement natural breast tissue. Composition includes a silicone outer layer with saline as the filler.

Silicone Gel-Filled Breast Implant: A device intended to be implanted in the breast area of the body to replace or supplement natural breast tissue. Composition includes a silicone outer layer with a silicone gel filler.

Toxic Shock Syndrome (TSS): A collection of signs and symptoms resulting from infection, often caused by Staphylococcal or Streptococcal bacteria. TSS is both rare and potentially life-threatening.

XIV. Data Tables

TABLE 1. Status of Allergan Natrelle and Mentor MemoryGel silicone gel-filled breast implant post-approval studies.

Study	Allergan		Mentor	
	Enrollment	**Follow Up**	**Enrollment**	**Follow Up**
Core Study	715 patients Enrollment Closed	At 10 years: Overall 65% Primary Aug. 66% Rev Aug. 64% Primary Recon. 75% Rev Recon. 80%	1008 patients Enrollment Closed	At 8 years: Overall 58% Primary Aug. 54% Rev Aug. 59% Primary Recon. 67% Rev Recon. 64%
Large Study	41,342* silicone patients (105% of target) and 15,646 saline patients (103% of target). Enrollment Closed	Below Target: 60.5% at year 2 for silicone; 45.1% at year 2 for saline	41,419** silicone patients (98.6% of target) and 1,030 saline patients (103% of target). Enrollment Closed	Below Target: 21.1% at year 3.for silicone; 9.6% at year 3 for saline
Device Failure Studies	Not Applicable***	No follow-up but study reports are due annually	Not Applicable***	No follow-up but study reports are due annually
Focus Group Study	52 patients Enrollment Closed	No Follow-up of Participants	35 patients Enrollment Closed	No Follow-up of Participants
Informed Decision Process Study	Annual Random Sample of 50 Physicians	No Follow-up of participants	Annual Random Sample of 50 Physicians	No Follow-up of participants
Adjunct Study****	Enrollment Closed	54% at 1-year 30% at 3-year 23% at 5-year	Enrollment Closed	36% at 1-year 24% at 3-year 16% at 5-year

* The enrollment for the Allergan *Large Study* silicone group includes at least 97 women in the augmentation cohorts who are younger than 22 years of age.

**The enrollment for the Mentor *Large Study* silicone group excludes 556 women in the augmentation cohorts who are younger than 22 years of age.

***No enrollment targets were set for the *Device Failure Studies*; all explanted and returned devices are included in these studies.

****The protocols for the *Adjunct Studies* did not include follow-up targets.

TABLE 2. Enrollment in the silicone gel-filled breast implant *Core Studies* by manufacturer and indication.

Company	Study Population	Primary Augmen-tation	Revision Augmen-tation	Primary Recon-struction	Revision Recon-struction	Total
Allergan	Overall	455	147	98	15	715
	MRI cohort	147	49	50	5	251
Mentor	Overall	552	145	251	60	1,008
	MRI cohort	202	56	134	28	420

TABLE 3. ***Core Study*** **complications and adverse outcomes over 10 years post-implantation for Allergan Natrelle silicone gel-filled breast implant patients. Table shows cumulative incidence rates over time and 95% confidence intervals calculated using Kaplan-Meier analysis*.**

Complication or Outcome	Primary Augmentation (N=455)	Revision Augmentation (N=147)	Primary Reconstruction (N=98)	Revision Reconstruction (N=15)
Asymmetry	3.3% (2.0-5.1)	6.5% (3.2-12.8)	23.2% (15.4-33.9)	6.7% (0.2-31.9)
Breast pain	10.9% (8.2-14.3)	11.7% (7.1-18.9)	6.8% (2.8-16.1)	0%
Breast/skin sensation changes	1.6% (0.8-3.3)	2.2% (0.7-6.6)	0%	0%
Bruising	0.4% (0.1-1.8)	3.0% (1.1-7.8)	1.0% (0.1-7.1)	6.7% (0.2-31.9)
Capsular contracture (Baker III/IV)	19.1% (15.6-23.3)	27.5% (20.3-36.6)	24.6% (16.2-36.2)	6.7% (0.2-31.9)
Delayed wound healing	1.1% (0.5-2.7)	0.7% (0.1-4.8)	1.0% (0.1-7.2)	0%
Hematoma	1.6% (0.7-3.2)	2.1% (0.7-6.3)	1.5% (0.2-10.4)	0%
Implant malposition	6.3% (3.9-8.4)	6.0% (3.1-11.7)	2.3% (0.6-8.9)	13.3% (1.7-40.5)
Implant palpability/visibility	1.9% (1.0-3.8)	6.0% (3.0-11.6)	6.5% (0.4-17.0)	6.7% (0.2-31.9)
Implant removal with or without replacement	20.8% (17.2-25.2-)	32.4% (25.0-41.3)	53.8% (43.65.3)	20% (4.3-48.1)
Implant rupture	10.1% (7.4-13.7)	6.3% (2.8-13.7)	27.2% (17.3-41.3)	6.7% (.2-31.9)
Infection	0.5% (0.1-2.1)	1.4% (0.3-5.4)	3.2% (1.0-9.5)	0%
Irritation	0%	0.7% (0.1-5.0)	0%	0%
Necrosis	0.2% (0-1.6%)	0%	2.3% (0.6-8.8)	0%
Nipple complications	6.3% (4.3-9.1)	1.4% (0.3-5.4)	3.3% (1.1-9.8)	0%
Ptosis	2.0% (1.0-3.9)	4.9% (2.2-10.5)	0%	0%
Redness	0.7% (0.2-2.0)	0.8% (0.1-5.2)	2.1% (0.5-8.3)	0%

Table 3 (continued).

Complication or Outcome	Primary Augmentation (N=455)	Revision Augmentation (N=147)	Primary Reconstruction (N=98)	Revision Reconstruction (N=15)
Reoperation	36.1% (31.6-40.9)	46.0% (38.0-54.9)	71.9% (61.5-81.4)	46.7% (21.3-73.4)
Scarring/hypertrophic scarring	4.2% (2.6-6.5)	6.6% (3.5-12.4)	5.5% (2.3-12.7)	0%
Seroma/fluid accumulation	1.8% (0.9-3.5)	6.0% (3.0-11.7)	2.4% (0.3-15.7)	6.7% (0.2-31.9)
Skin rash	0.9% (0.3-2.3)	0.7% (0.1-4.9)	2.1% (0.5-7.9)	6.7% (0.2-31.9)
Swelling	9.2% (6.8-15.0)	8.3% (4.6-14.5)	7.1% (3.5-14.4)	0%
Wrinkling	1.8% (0.8-3.7)	5.4% (2.6-11.0)	10.2% (5.2-19.6)	0%

* The number of patients evaluated at the 10 year follow-up were: 269 (primary augmentation), 74 (revision augmentation), 44 (primary reconstruction), and 8 (revision reconstruction).

TABLE 4. ***Core Study*** **complications and adverse outcomes over 8 years post-implantation for Mentor MemoryGel silicone gel-filled breast implant patients. Table shows cumulative incidence rates over time and 95% confidence intervals calculated using Kaplan-Meier analysis*.**

Complication or Outcome	Primary Augmentation (N=552)	Revision Augmentation (N=145)	Primary Reconstruction (N=251)	Revision Reconstruction (N=60)
Breast mass	5.4% (3.7-7.8)	6.5% (3.4-12.0)	5.2% (2.9-9.3)	7.2% (2.8-18.2)
Breast pain	2.5% (1.5-4.3)	3.4% (1.3-8.8)	2.8% (1.2-6.2)	5.2% (1.7-15.3)
Breast/skin sensation changes	2.8% (1.7-4.5)	1.4% (0.4-5.4)	0%	1.8% (0.3-12.0)
Capsular contracture (Baker II)	2.0% (1.1-3.7)	6.2% (3.1-12.1)	4.4% (2.3-8.3)	4.0% (1.0-15.2)
Capsular contracture (Baker III/IV)	10.9% (8.5-13.9)	24.1% (17.7-32.3)	15.3% (11.1-20.9)	23.1% (14.1-36.6)
Delayed wound healing	0%	2.1% (0.7-6.3)	0%	1.7% (0.2-11.3)
Dog ear scars from mastectomy	0%	0%	1.6% (0.6-4.3)	3.4% (0.9-12.8)
Granuloma	0%	2.4% (0.8-7.4)	0%	5.0% (1.6-14.7)
Hematoma	2.9% (1.8-4.8)	2.8% (1.1-7.2)	1.3% (0.4-3.9)	3.4% (0.9-13.0)
Implant extrusion	0%	1.4% (0.4-5.5)	1.2% (0.4-3.7)	1.7% (0.2-11.3)
Implant malposition	0%	2.5% (0.8-7.9)	2.6% (1.2-5.8)	6.7% (2.6-16.9)
Implant removal with or without replacement	7.3% (5.3-9.9)	21.1% (15.0-29.2)	23.3% (18.2-29.4)	29.0% (19.1-42.5)
Implant rupture **	13.6% (7.6-23.6)	15.5% (6.5-34.6)	14.0% (7.6-25.0)	21.3% (7.3-53.3)
Infection	1.6% (0.9-3.1)	1.4% (0.4-5.5)	6.2% (3.8-10.2)	0%
Inflammation of breast	0%	1.4% (0.4-5.5)	0%	1.7% (0.2-11.4)
Lactation difficulties	2.0% (1.1-3.8)	1.6% (0.4-6.1)	0%	0%

Table 4 (continued).

Complication or Outcome	Primary Augmentation (N=552)	Revision Augmentation (N=145)	Primary Reconstruction (N=251)	Revision Reconstruction (N=60)
Metastatic disease	0%	0%	5.7% (3.3-9.6)	4.0% (1.0-15.2)
Miscarriage	2.9% (1.8-4.8)	2.5% (0.8-7.6)	2.3% (1.0-5.6)	0%
New diagnosis of breast cancer	0%	1.8% (0.5-7.2)	1.9% (0.7-5.1)	1.7% (0.2-11.4)
New diagnosis of rheumatic disease	1.8% (1.0-3.5)	1.7% (0.4-6.5)	2.6% (1.1-6.2)	3.4% (0.9-12.9)
Nipple complications	0%	0%	1.3% (0.4-4.1)	0%
Nipple sensation changes	11.8% (9.3-14.8)	14.6% (9.7-21.8)	2.1% (0.9-5.0)	1.7% (0.2-11.3)
Pre-eclampsia at 36 weeks pregnant	0%	1.1% (0.2-7.4)	0%	0%
Reoperation	20.1% (17.0-23.8)	37.8% (30.2-46.6)	38.8% (32.9-45.5)	40.8% (29.5-54.5)
Seroma	1.1% (0.5-2.5)	2.1% (0.7-6.3)	4.8% (2.8-8.4)	1.7% (0.2-11.3)

* The number of patients evaluated at the 10 year follow-up were: 291 (primary augmentation), 77 (revision augmentation), 151 (primary reconstruction), and 36 (revision reconstruction).

** Rupture rates were estimated in MRI cohort at 8 years post-implantation.

TABLE 5. Comparison of rates of key complications and outcomes in the *Core Studies* at the time of approval and at the 10-year follow-up for the Allergan Natrelle silicone gel-filled breast implant patients. Table shows cumulative incidence rates over time and 95% confidence intervals calculated using Kaplan-Meier analysis.

	Allergan	
Complication or Outcome by Study Cohort	**4-year FU Rate (%)**	**10-year FU Rate (%)**
Capsular Contracture		
Primary Augmentation	13.2 (10.0-16.3)	19.1 (15.6-23.3)
Revision Augmentation	17.0 (10.7-23.4)	27.5 (20.3-36.6)
Primary Reconstruction	14.1 (7.0-21.2)	24.6 (16.2-36.2)
Revision Reconstruction	6.7 (0.2-31.9)	6.7 (0.2-31.9)
Reoperation		
Primary Augmentation	23.5 (19.5-27.5)	36.1 (31.6-40.9)
Revision Augmentation	35.3 (27.3-43.4)	46.0 (38.0-54.9)
Primary Reconstruction	40.9 (31.0-50.8)	71.9 (61.5-81.4)
Revision Reconstruction	33.3 (11.8-61.6)	46.7 (21.3-73.4)
Removal		
Primary Augmentation	9.6 (6.8-12.4)	20.8 (17.2-25.2)
Revision Augmentation	13.3 (7.6-19.0)	32.4 (25.0-41.3)
Primary Reconstruction	24.8 (15.9-33.6)	53.8 (43.65.3)
Revision Reconstruction	0	20.0 (4.3-48.1)

TABLE 6. Comparison of rates of key complications and outcomes in the *Core Studies* at the time of approval and at the 8-year follow-up for the Mentor MemoryGel silicone gel-filled breast implant patients. Table shows cumulative incidence rates over time and 95% confidence intervals calculated using Kaplan-Meier analysis.

	Mentor	
Complication or Outcome by Study Cohort	**3-year FU Rate (%)**	**8-year FU Rate (%)**
Capsular Contracture		
Primary Augmentation	8.1 (5.8-10.4)	10.9 (8.5-13.9)
Revision Augmentation	18.9 (12.5-25.4)	24.1 (17.7-32.3)
Primary Reconstruction	8.3 (4.7-11.9)	15.3 (11.1-20.9)
Revision Reconstruction	16.3 (5.0-27.6)	23.1 (14.1-36.6)
Reoperation		
Primary Augmentation	15.4 (12.3-18.4)	20.1 (17.0-23.8)
Revision Augmentation	28.0 (20.4-35.6)	37.8 (30.2-46.6)
Primary Reconstruction	27.0 (21.4-32.6)	38.8 (32.9-45.5)
Revision Reconstruction	29.1 (17.4-40.7)	40.8 (29.5-54.5)
Removal		
Primary Augmentation	4.9 (3.1-6.7)	7.3 (5.3-9.9)
Revision Augmentation	13.4 (7.5-19.3)	21.1 (15.0-29.2)
Primary Reconstruction	12.7 (8.5-16.9)	23.3 (18.2-29.4)
Revision Reconstruction	13.7 (4.9-22.6)	29.0 (19.1-42.5)

TABLE 7. Primary reasons for implant removal for Allergan Natrelle silicone gel-filled breast implants in the *Core Study* through 10 years. Table shows the number of times the reason was reported as the primary reason for removal and the percentage of the total number of reasons for removal within each cohort.

Reason for Removal	Primary Augmentation (N=156*)	Revision Augmentation (N=78*)	Primary Reconstruction (N=56*)	Revision Reconstruction (N=3*)
Asymmetry	7 (4.5%)	1 (1.3%)	12 (21.4%)	2 (66.7%)
Breast cancer mass	2 (1.3%)	2 (2.6%)	0	0
Breast pain	5 (3.2%)	1 (1.3%)	0	0
Breast tissue contour Deformity	1 (0.6%)	0	0	0
Capsular contracture	50 (32.1%)	28 (35.9%)	10 (17.9%)	1 (33.3%)
Hematoma/seroma	0	0	1 (1.8%)	0
Implant extrusion	1 (0.6%)	1 (1.3%)	1 (1.8%)	0
Implant malposition	11 (7.1%)	14 (18.0%)	11 (19.6%)	0
Implant rupture	27 (17.3%)	6 (7.7%)	15 (26.8%)	0
Infection	2 (1.3%)	2 (2.6%)	0	0
Necrosis	0	0	1 (1.8%)	0
Need for biopsy	1 (0.6%)	0	0	0
Patient request for style/size change	31 (19.9%)	11 (14.1%)	4 (7.1%)	0
Ptosis	12 (7.7%)	6 (7.7%)	0	0
Scarring	0	2 (2.6%)	0	0
Wrinkling/rippling	6 (3.9%)	2 (2.6%)	1 (1.8%)	0

* Total number of implant removals in each cohort.

TABLE 8. Primary reasons for implant removal for Mentor MemoryGel silicone gel-filled breast implants in the *Core Study* through 8 years. Table shows the number of times the reason was reported as the primary reason for removal and the percentage of the total number of reasons for removal within each cohort.

Reason for Removal	Primary Augmentation (N=68*)	Revision Augmentation (N=51*)	Primary Reconstruction (N=74*)	Revision Reconstruction (N=2*)
Asymmetry	1 (1.5%)	2 (3.9%)	15 (20.3%)	3 (13.6%)
Breast pain	3 (4.4%)	0	2 (2.7%)	1 (4.5%)
Capsular contracture (Baker II/III/IV)	13 (19.1%)	15 (29.4%)	11 (14.9%)	5 (22.7%)
Hematoma	0	0	1 (1.4%)	0
Infection	2 (2.9%)	1 (2.0%)	2 (2.7%)	0
Implant Extrusion	0	1 (2.0%)	2 (2.7%)	1 (4.5%)
Implant malposition	0	0	4 (5.4%)	0
Implant rupture	3 (4.4%)	4 (7.8%)	8 (10.8%)	1 (4.5%)
Necrosis	2 (2.9%)	0	0	0
Patient request for style/size change	36 (52.9%)	18 (35.3%)	17 (23.0%)	5 (22.7%)
Ptosis	0	0	1 (1.4%)	0
Wrinkling	1 (1.5%)	0	0	1 (4.5%)
Other	7 (10.3%)	9 (17.6%)	11 (14.9%)	5 (22.7%)

* Total number of implant removals in each cohort.

TABLE 9. Primary Reasons for Reoperation for Allergan Natrelle Silicone Gel- filled Breast Implants in the *Core Study* through 10 years. Table shows the number of times the reason was reported as the primary reason for reoperation and the percentage of the total number of reasons for reoperation within each cohort.

Reason for Reoperation*	Primary Augmentation (N=221**)	Revision Augmentation (N=108**)	Primary Reconstruction (N=93**)	Revision Reconstruction (N=12**)
Asymmetry	5 (2.3%)	3 (2.8%)	15 (16.1%)	2 (16.7%)
Breast cancer mass	4 (1.8%)	3 (2.8%)	3 (3.2%)	0
Breast pain	3 (1.4%)	1 (0.9%)	0	0
Breast tissue contour Deformity	0	1 (0.9%)	2 (2.2%)	0
Capsular contracture	55 (24.9%)	26 (24.1%)	12 (12.9%)	2 (16.7%)
Delayed wound healing	3 (1.4%)	2 (1.9%)	1 (1.1%)	0
Device injury -- iatrogenic or traumatic	0	1 (0.9%)	0	0
Extrusion	1 (0.5%)	1 (0.9%)	2 (2.2%)	0
Hematoma/seroma	13 (5.9%)	13 (12.0%)	8 (8.6%)	0
Implant malposition	27 (12.2%)	12 (11.1%)	15 (16.1%)	0
Implant palpability/visibility	1 (0.5%)	1 (0.9%)	0	0
Implant rupture	29 (13.1%)	7 (6.5%)	14 (15.1%)	0
Infection	2 (0.9%)	3 (2.8%)	0	0
Necrosis	1 (0.5%)	0	1 (1.1%)	0
Need for biopsy	28 (12.7%)	9 (8.3%)	8 (8.6%)	1 (8.3%)
Nipple complications	1 (0.5%)	3 (2.8%)	1 (1.1%)	5 (41.7%)
Patient request for style/size change	12 (5.4%)	3 (2.8%)	3 (3.2%)	0
Ptosis	25 (11.3%)	9 (8.3%)	4 (4.3%)	1 (8.3%)
Scarring	8 (3.6%)	7 (6.5%)	3 (3.2%)	1 (8.3%)
Wrinkling/rippling	3 (1.4%)	2 (1.9%)	1 (1.1%)	0

* When reoperations were performed for multiple reasons, a hierarchy was used to determine the primary reason.

** Total number of reoperations in each cohort.

TABLE 10. Primary Reasons for Reoperation for Mentor MemoryGel Silicone Gel-filled Breast Implants in the *Core Study* through 8 years. Table shows the number of times the reason was reported as the primary reason for reoperation and the percentage of the total number of reasons for reoperation within each cohort.

Reason for Reoperation*	Primary Augmentation (N=146**)	Revision Augmentation (N=78**)	Primary Reconstruction (N=123**)	Revision Reconstruction (N=38**)
Asymmetry	5 (3.4%)	1 (1.3%)	20 (16.3%)	2 (5.3%)
Abnormal screening	1 (0.7%)	0	0	0
Breast cancer	0	1 (1.3%)	1 (0.8%)	0
Breast mass	13 (8.9%)	9 (11.5%)	14 (11.4%)	7 (18.4%)
Breast pain	1(0.7%)	0	2 (1.6%)	1 (2.6%)
Capsular contracture (Baker II/III/IV)	44 (30.1%)	24 (30.8%)	18 (14.6%)	5 (13.2%)
Calcification	2 (1.4%)	0	0	0
Capsular tear	1 (0.7%)	0	0	1 (2.6%)
Delayed wound healing	1 (0.7%)	5 (6.4%)	0	0
Extrusion/Necrosis	2 (1.4%)	2 (2.6%)	2 (1.6%)	1 (2.6%)
Hematoma/Seroma	12 (8.2%)	5 (6.4%)	4 (3.2%)	1 (2.6%)
Implant malposition	4 (2.7%)	1 (1.3%)	8 (6.5%)	0
Implant rupture	2 (1.4%)	4 (5.1%)	10 (8.1%)	1 (2.6%)
Infection	3 (2.1%)	1 (1.3%)	3 (2.4%)	0
Nipple complications	0	0	1 (0.8%)	0
Patient request for style/size change	20 (13.7%)	11 (14.1%)	11 (8.9%)	4 (10.5%)
Ptosis	4 (2.7%)	2 (2.6%)	4 (3.3%)	3 (7.9%)
Scarring/hypertrophic scarring	16 (11.0%)	3 (3.8%)	4 (3.3%)	0
Suture complication	1 (0.7%)	0	1 (0.8%)	0
Wrinkling/rippling	1 (0.7%)	1 (1.3%)	0	1 (2.6%)

* When reoperations were performed for multiple reasons, a hierarchy was used to determine the primary reason.

** Total number of reoperations in each cohort.

TABLE 11. Allergan *Large Post-Approval Study* of Natrelle silicone gel-filled breast implants: summary of enrolled participants by indication. Table shows the number of participants in each cohort and the percentage that each cohort contributes to the total number of participants for each implant type.

Indication	Silicone (N=41,342)	Saline (N=15,646)	Total Number of Participants (N=56,988)
Primary Augmentation*	29,886 (72.3%)	14,447 (92.3%)	44,333 (77.8%)
Revision Augmentation	6,033 (14.6%)	970 (6.2%)	7,003 (12.3%)
Primary Reconstruction	4,714 (11.4%)	184 (1.2%)	4,898 (8.6%)
Revision Reconstruction	709 (1.7%)	44 (0.3%)	753 (1.3%)
Missing	0	1 (<0.1%)	1 (<0.1%)

* Allergan is still in the process of examining and reporting the number of augmentation patients younger than 22 years of age. The augmentation numbers listed in this table include at least 97 women who were younger than the qualifying age for this study (22 or older).

TABLE 12. Mentor *Large Post-Approval Study* of MemoryGel silicone gel-filled breast implants: summary of enrolled participants by indication. Table shows the number of participants in each cohort and the percentage that each cohort contributes to the total number of participants for each implant type.

Indication	Silicone (N=41,975)	Saline (N=1,030)	Total Number of Participants (N=43,005)
Primary Augmentation	26,118 (62.2%)	930 (90.3%)	27,048 (62.9%)
Revision Augmentation	8,365 (19.9%)	76 (7.4%)	8,441 (19.6%)
Primary Reconstruction	5,031 (12.0%)	13 (1.3%)	5,042 (11.7%)
Revision Reconstruction	1,757 (4.2%)	9 (0.9%)	1,766 (4.1%)
Missing	148 (0.4%)	2 (0.2%)	150 (0.3%)
Augmentation patients younger than age 22	556 (1.3%)	0 (0%)	556 (1.3%)

TABLE 13. Primary reason for explantation for Allergan Natrelle silicone gel-filled breast implants in the *Large Post-Approval Study* (by implant). Investigator reports contain numbers reported by physicians after clinical evaluation. Patient reports come from patient survey data.

Reason for Explantation	Number of Explants (Investigator Report at Year 1) (N=1310*)	Number of Explants (Patient Report at Year 1) (N=926*)	Number of Explants (Patient Report at Year 2) (N=350*)
Suspected rupture	35 (2.7%)	25 (2.3%)	15 (4.3%)
Infection	79 (6.0%)	78 (8.4%)	27 (7.7%)
Capsular contracture	128 (9.8%)	184 (19.9%)	77 (22.0%)
Implant malposition	119 (9.1%)	110 (11.9%)	48 (13.7%)
Ptosis	38 (2.9%)	69 (7.5%)	13 (3.7%)
Desire for size/style change	664 (50.7%)	299 (32.3%)	118 (33.7%)
Other	247 (18.9%)	161 (17.4%)	52 (14.9%)

* Total number of implant removals.

TABLE 14. Primary reason for explantation during 3 years after implantation for Mentor MemoryGel silicone gel-filled breast implants in the *Large Post-Approval Study*.

Reason for Removal	Primary Augmentation (N=420*)	Revision Augmentation (N=293*)	Primary Reconstruction (N=454*)	Revision Reconstruction (N=145*)
Asymmetry	21 (5.0%)	39 (13.3%)	108 (23.8%)	37 (25.5%)
Capsular contracture (Baker II/III/IV)	14 (3.3%)	16 (5.5%)	21 (4.6%)	6 (4.1%)
Capsular tear	0	0 (0.0%)	2 (0.4%)	0
Implant palpability	2 (0.5%)	1 (0.3%)	0	0
Implant removal	5 (1.2%)	7 (2.4%)	2 (0.4%)	3 (2.1%)
Implant rupture	7 (1.7%)	12 (4.1%)	2 (0.4%)	0
Lack of projection	0	6 (2.0%)	12 (2.6%)	3 (2.1%)
Position change (dissatisfaction)	3 (0.7%)	0 (0.0%)	4 (0.9%)	3 (2.1%)
Ptosis	1 (0.2%)	1 (0.3%)	2 (0.4%)	0
Size change – patient request	169 (40.2%)	91 (31.1%)	92 (20.3%)	18 (12.4%)
Size change – physician assessment	5 (1.2%)	2 (0.7%)	20 (4.4%)	4 (2.8%)
Symmastia	0	0	2 (0.4%)	0
Wrinkling	2 (0.5%)	3 (1.0%)	9 (2.0%)	4 (2.8%)
Breast pain not associated with other complications	3 (0.7%)	2 (0.7%)	4 (0.9%)	2 (1.4%)
Extrusion	11 (2.6%)	14 (4.8%)	32 (7.0%)	9 (6.2%)
Necrosis	0	0	3 (0.7%)	0
Hematoma	1 (0.2%)	1 (0.3%)	0	0
Irritation/Inflammation	3 (0.7%)	0	0	0
Seroma	1 (0.2%)	7 (2.4%)	1 (0.2%)	1 (0.7%)
Infection	37 (8.8%)	23 (7.8%)	34 (8.2%)	9 (6.7%)
New diagnosis of Breast cancer	1 (0.2%)	0	2 (0.4%)	0

Table 14 (continued).

Reason for Removal	Primary Augmentation (N=420*)	Revision Augmentation (N=293*)	Primary Reconstruction (N=454*)	Revision Reconstruction (N=145*)
New diagnosis of rheumatic disease	0	0	1 (0.2%)	0
Unknown	131 (31.2%)	76 (25.9%)	113 (24.9%)	52 (35.9%)
Other	14 (3.3%)	13 (4.4%)	5 (1.1%)	1 (0.7%)

* Total number of implant removals

TABLE 15. MDR reports of patient problems (based on Patient Problem Codes) with silicone gel-filled breast implants, ranked by frequency of reporting.*

Rank	Patient Problem Code Reported**	Number of Times the Problem Code was Used	Percent of the Total Number of Problem Codes Used (N=530)
1	Surgical Procedure (generally replacement or removal)	78	15.7
2	Pain	66	12.5
3	Rash/hives/itching/burning sensation	36	6.8
4	Capsular Contracture	33	6.2
5	Therapy/non-surgical treatment	26	4.9
6	Fatigue/weakness	25	4.7
7	Arthralgia/arthritis/myalgia	22	4.2
8	Swelling/edema	22	4.2
9	Palpitations/chest pain	15	2.8
10	Scarring/numbness	14	2.8
11	Disability	9	1.7
12	Infection	9	1.7
13	Breathing difficulties	9	1.7

* Reporting period: November 17, 2006 to December 31, 2010

** One report may contain multiple patient problem codes. A total of 530 "Patient Problem Codes" were used in 133 reports. Coding of reports increases the ability to accurately collect, categorize, and compare information within and across reporting and data collection systems. For reports required by FDA, the reporter assigns the patient and device problem codes.

TABLE 16. MDR reports of device problems (based on Device Problem Codes) with silicone gel-filled breast implants, ranked by frequency of reporting.*

Rank	Device Problem Code Reported**	Number of Times the Problem Code was Used	Percent of the Total Number of Problem Codes Used (N=239)
1	Implant removed (both to treat complications and remove at woman's request to change implant size or shape)	70	30.1
2	Rupture	62	26.0
3	Implant replaced	36	15.0
4	Device or device fragment remains in patient	24	10.1
5	Sterility/foreign material	4	1.7
6	Migration of device or device component	3	1.3
7	Implant Extrusion Displacement/Malposition of device	3	1.3

* Reporting period: November 17, 2006 to December 31, 2010

** One report may contain multiple device problem codes. A total of 239 patient problem codes were used in 133 reports. Coding of reports increases the ability to accurately collect, categorize, and compare information within and across reporting and data collection systems. For reports required by FDA, the reporter assigns the patient and device problem codes.

TABLE 17. PSR reports of patient problems (based on Patient Problem Code frequency of 1% or greater) with silicone gel-filled breast implants.* Ranked by frequency of reporting.

Rank	Patient Problem Code**	Number of Times Problem Code was Used	Percent of the Total Number of Problem Codes Used (N=26,511)
1	Surgical Procedure	7,800	29.4
2	Capsular Contraction	4983	18.8
3	Pain	2695	10.2
4	Infection	1,001	3.8
5	Breast lumps	990	3.7
6	Reynaud's phenomenon	364	1.4
8	Inflammation	341	1.3
9	Cancer, Other	331	1.2
10	No consequence to patient	313	1.2
11	Wrinkling	312	1.2
	Other	2558	9.6
	Patient condition unknown	4823	18.2

* Reporting period: November 17, 2006 to December 31, 2010

** One report may contain multiple patient problem codes. A total of 26,511 patient problem codes were used in 16,681 reports. Coding of reports increases the ability to accurately collect, categorize, and compare information within and across reporting and data collection systems. This facilitates the analysis of potential safety and effectiveness issues and the assessment of trends within a product category.

At the time PSR was authorized, the agency defined the types of events that could be submitted under the PSR program and provided the silicone gel-filled breast implants manufacturers with a set of specific patient problem codes and device problem codes to be used for PSR reports. Like all coding systems, accuracy and reliability of coded information depends on the correct assignment of the codes.

TABLE 18. PSR reports of device problems (based on Device Problem Code frequency of 1% or greater) with silicone gel-filled breast implants.* Ranked by frequency of reporting.

Rank	Device Problem Code**	Number of Times Problem Code was Used	Percent of the Total Number of Problem Codes Used (N=12,327)
1	Device-patient incompatibility	4860	39.4
2	Rupture	4541	36.8
3	Malposition	903	7.3
4	Tears, rips, holes in devices or device material (device never implanted), out of box failure	244	3.1
5	Wrinkling or folds	288	2.3
6	Visibility or palpability	200	1.6
	Other	1157	9.4

*Reporting period: November 17, 2006 to December 31, 2010

** One report may contain multiple device problem codes. A total of 12,327 device problem codes were used in 16,681 reports. Coding of reports increases the ability to accurately collect, categorize, and compare information within and across reporting and data collection systems. This facilitates the analysis of potential safety and effectiveness issues and the assessment of trends within a product category.

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A manufacturer promised "quality without compromise". Instead he used industrial ingredients — and hundreds of thousands of women are at risk

THE GREAT FRENCH BREAST IMPLANTS SCANDAL

REUTERS/ERIC GAILLARD

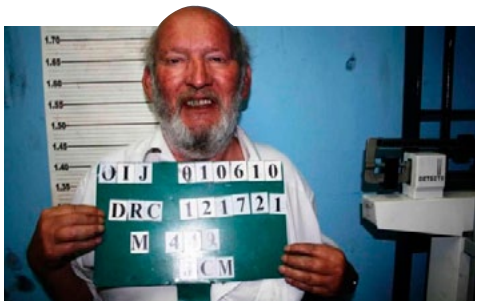
FAULTY GOODS: A defective silicone gel breast implant manufactured by PIP after it was removed from a patient in a clinic in Nice late last year

BY ALEXANDRIA SAGE, NATALIE HUET AND JEAN-FRANCOIS ROSNOBLET
MARSEILLE, FRANCE, FEBRUARY 2

In March 2010, a pair of health inspectors acting on a tip paid a three-day visit to a factory in this hilly town on the Mediterranean coast.

The factory was the headquarters of Poly Implant Prothese (PIP), a leading international maker of breast implants founded by French entrepreneur Jean-Claude Mas. The inspectors found something odd: six discarded plastic containers of Silopren, a liquid silicone designed for industrial, not medical use, lined up along the outside wall of the production site.

A week later, gendarmes descended on the plant. Mas skipped out just ahead of them, eluding interrogation for nearly eight months, but his game was up. In the nearly two years since, the cheap silicone used in PIP's fake breasts has continued to leach into women's bodies. In France, 1,262 of the roughly 300,000 breast implants the company sold



REUTERS/INTERPOL/HANDOUT

GAMBLER: Jean-Claude Mas as he appears on a "red notice" posted by Interpol after a driving offense in Costa Rica . His lawyer says he cut corners to save money

REUTERS/BENOIT TESSIER

RECONSTRUCTION: Paris-based plastic surgeon Isabelle Sarfati chose PIP implants for breast cancer survivors before stopping due to higher rupture rates.

worldwide have split open in the past two years. PIP has been closed down, Mas has been arrested and put under investigation for alleged bodily harm, and French and European safety regulators have been thrust into an uncomfortable spotlight.

Mas, 72, a grocer's son from the south of France, had no scientific training. Yet for the first decade of this century he was able to manufacture and sell faulty breast implants on international markets that he and some of his employees knew to be substandard, according to testimony given to French police and seen by Reuters.

The history of breast implants is littered with flawed devices, a colourful cast of intertwined players and billion-dollar lawsuits. Reuters reviewed hundreds of pages of police investigation transcripts and financial documents, and interviewed former PIP employees, the company's suppliers, customers and health experts, to piece together this latest chapter in that history.

It is a tale of a haphazardly run and cash-strapped company that allegedly took desperate and sometimes deceptive steps to shave costs and hide the true ingredients of its devices. PIP's efforts were made easier by a European regulatory regime that had been essentially outsourced to the very companies that are meant to be regulated.

> **"Maybe it's shameful, but there you go. We live in a capitalist world."**

Among the new details to emerge: PIP was able to save an estimated 1.2 million euros ($1.6 million) in one year by using the industrial-grade silicone in its implants, according to figures cited by police investigators. And it relied on crude, unscientific tests of product quality, such as judging silicone gel by sticking a finger in it, according to one former worker. Some 75 percent of its implants used the non-approved, cheaper gel, Mas told police.

"Maybe it's shameful, but there you go," Yves Haddad, a lawyer who represents both Mas and his now-defunct company, told Reuters at the end of December. "We live in a capitalist world."

Mas, who declined to comment for this story, has said his products are harmless. After the health ministry advised Frenchwomen to have the devices removed, he told French radio network RTL last month that the decision was "criminal" and the health minister "needs to be committed."

A CAREER IN SALES

Jean-Claude Florent Mas, born in Tarbes, near the Spanish border, was a salesman by temperament. He sold everything from life insurance to wine and dental equipment. He entered health care in the mid-1960s, working for various labs, including one that was bought by Bristol-Myers in the 1970s, where he stayed until 1980 as a salesman in the south of France. Mas' attorney, Haddad, says his client was one of the firm's top salesmen, although Bristol-Myers could not confirm that or say why he left.

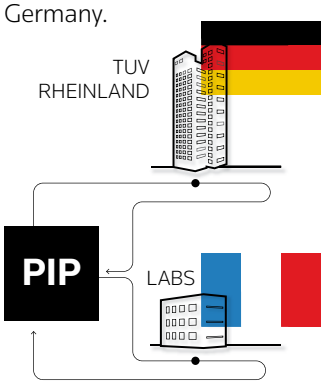
It was after Bristol-Myers that Mas got involved in breast implants. He began working with a French plastic surgeon, Henri Arion, who had made France's first breast implant in 1965, and was now selling saline implants under the name Simaplast.

It wasn't a great start. Simaplast's implants eventually were found to be prone to rupture, according to a 1999 study by U.S. non-profit Institute of Medicine. Simaplast morphed into a company named MAP - the precursor to PIP - where Mas said he performed every job from production to sweeping the floors. The small group of employees included a woman, Dominique Lucciardi, who would become Mas' companion and mother of his two children. They would take turns filling

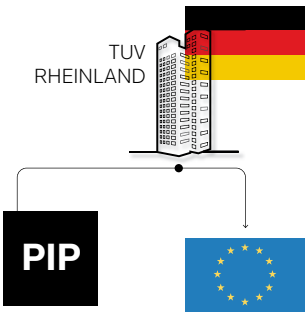
DANGEROUS LOOPHOLES

French police have arrested PIP boss Jean-Claude Mas for alleged bodily harm in a breast implant scandal. But some doctors, regulators and the medical devices industry itself say Europe's weak regulatory system is also at fault.

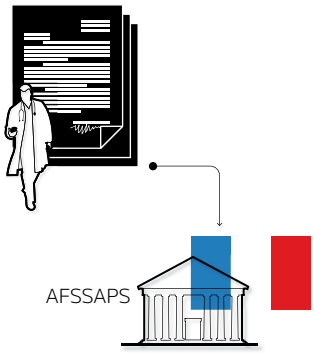
France has a medical regulator, AFSSAPS, but it doesn't vet new devices. European nations entrust that work to one of between 70 and 80 Notified Bodies in Europe. In PIP's case, it was TUV Rheinland of Germany.



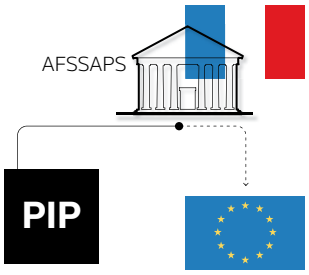
TUV Rheinland certifies the PIP breast implant for sale in the E.U. American regulators reject the device, but European sales continue for years.



Surgeons in France begin complaining to France's AFSSAPS about high rupture rates in PIP implants.



After an on-site inspection, AFSSAPS takes the product off the market in France and alerts other authorities.



AT ISSUE

TUV does minimal oversight. It merely reviews paperwork and test results submitted by the maker. PIP allegedly lied about its implant ingredients – including low-grade silicone.

the prostheses, he told police.

In 1991, aged 52, Mas launched PIP, a limited liability company and chose as its headquarters the site of the old Simaplast factory. In preparation, he had applied for a patent to sell implants containing silicone covered in polyurethane foam, he told police.

As he launched PIP, a breast implant scandal involving Dow Corning was sweeping across the United States. The American firm was found to have knowingly concealed safety concerns about its implants, and in 1992, the U.S. Food and Drug Administration called for a moratorium on the devices. Four years into PIP's life, in 1995, France also banned silicone in breast implants, a ban that ended in 2001.

Mas found that by innovating, he could still bring products to market. He switched to implants filled with saline solution and launched a pre-filled version; other brands needed to be filled while the patient was on the operating table. PIP's new product saved time, and surgeons liked it. PIP moved into the huge U.S. market in 1996, and soon the United States made up 40 percent of its revenue, according to company records.

AN ASYMMETRIC APPROACH

Opportunities for PIP grew on its home turf in 2001, when France lifted its ban on silicone implants, and the United States slowly began to approve more versions containing silicone gel, for which Mas already had a formula. "When I started PIP I brought this formula that I had kept," he told police. "Why change it?"

Regulators had never examined nor approved that filler, but Mas insisted to his staff that it was perfectly safe, his ex-employees told Reuters.

Building on his innovations in saline implants, in 2002 Mas brought a new twist to silicone by launching an asymmetrical product that became popular with surgeons and patients, because it gave a more natural look than the "classic" style of implant, which resembled a perfectly round orb.

PIP's approach to filling these implants was novel. On paper, the company said it used NuSil, a silicone blend made by a California company of the same name, which can be used in medical applications, including implantable devices. NuSil was founded by PIP's former U.S. distributor, Donald McGhan, who is now in prison in Texas for an unrelated fraud conviction. The company has declined any comment on the PIP affair.

But in reality, PIP was mostly using Mas' own non-approved PIP gel, which looked and felt exactly like NuSil, but cost a seventh of the price.

A litre of NuSil cost about 35 euros, versus 5 euros for PIP's version, Thierry Brinon, PIP's former technology head in charge of research and development, told police. Each implant on average used 330 cubic centimetres of gel. That meant it cost 11.55 euros to fill an implant with NuSil and a mere 1.65 euros to use PIP's gel, a difference of 9.90 euros on each implant produced.

Claude Couty, the former chief financial officer of PIP, told police it cost an average total of 38 to 42 euros to manufacture an implant filled with PIP gel, versus 52 for an

implant filled with NuSil. Investigators in the legal case file estimated that in one year alone, 2009, using PIP gel instead of NuSil saved the company nearly 1.2 million euros.

PIP sold implants to French surgeons for about 300 euros a piece. Abroad, the asking price was about 100 euros, according to former PIP staff and surgeons.

"This formula is perfect," Mas told police. "It's better than the formula for making NuSil."

DECEIVING INSPECTORS

But because NuSil was a known quantity and his gel recipe was not, Mas concealed the implants' ingredients from the regulator. Flaws in Europe's regulatory system gave him a helping hand.

France has a government regulator, the Agence Francaise de Securite Sanitaire des Produits de Sante, or AFSSAPS, which has the power to remove products from the market but does not certify them. But the agency that certified PIP's implants was actually a private company, based in Germany. TUV Rheinland first approved PIP's saline implants in 1997. Its officials paid annual visits to the factory in La-Seyne-sur-Mer and announced them 10 days in advance, in accordance with European guidelines.

That gave PIP plenty of time to hide the truth. Ahead of TUV visits, workers would clear away evidence of the cheaper silicones PIP was using and put together a doctored version of documents that included no references to the use of unapproved silicone, Mas and ex-managers told police. All internal communications related to TUV's visits were oral, said one former worker.

"Since 1997, we automatically hid the products that allowed us to make the PIP gel," Mas told police, according to notes in the case file, "because I knew they weren't regulation." In his second police interview, Mas said he had given "the order to hide the truth from TUV" since 1993.

TUV sued PIP in February 2011, saying PIP had tarnished its reputation by using TUV's name to market sub-standard products and that it had been systematically misled.

A HELPFUL LOOPHOLE

There were other gaps in the regulations that helped PIP keep its products on the market for so long. The system does not require on-site, unannounced checks of the implants' contents. Nor does it require that the chemical composition of the implants, once approved, be re-tested.

A TUV spokesman said it would only have made an unannounced visit for checks if there were very serious indications that something was amiss. There have been no cases of unannounced checks in Germany in the past 40 years, he added.

Moreover, TUV's yearly audits are essentially audits of overall processes; they do not perform on-site lab tests. The German company believes PIP deliberately deceived it.

AFSSAPS said it tested the insides of PIP's implants in 2001 to make sure they were what PIP said they were when silicone breast implants were allowed back onto the French market.

After 2001, however, that job went to two independent French laboratories: LEMI, Laboratoire d'Evaluation des Materiels Implantables and LNE, Laboratoire National de Metrologie et d'Essais. Mas told police the laboratories performed tests in 2002 and 2008.

AFSSAPS' deputy director general, Francois Hebert, told Reuters these tests were likely ordered by PIP following requests from surgeons, who may have sent back defective implants and asked for further evaluation.

LNE said its tests were mechanical — how likely PIP's implants were to resist pressure, for instance — but declined to provide further information. LEMI said its tests related to toxicity, but also declined to provide further information.

The first random test by AFSSAPS would not come until mid-2010 by which time PIP was under investigation by police. That was when AFSSAPS issued a report which said, "this one does not reach the degree of quality of a silicone gel intended for breast implants."

This week, France's health department and

REUTERS/ERIC GAILLARD

RUPTURED: A PIP silicone gel implant after its removal from a patient

REUTERS/JEAN-PAUL PELISSIER

CANDID: Jean-Claude Mas' lawyer Yves Haddad says his client is worn out. "This is a businessman who has been around. I'm even surprised he's still here"

AFSSAPS submitted a report to the country's health minister acknowledging gaps in the French and European regulatory system. The report cited the lack of unannounced visits and on-site testing of implants but said that PIP's alleged fraud was so sophisticated that "it's not evident that an inspection, even an unannounced one, could have been effective."

NO QUESTIONS ASKED?

The raw silicone materials for the PIP-formula gel included different products: Silopren – which was kept in the containers that had been spotted by inspectors - and Baysilone. PIP bought these silicone oils from a German distributor, Brenntag. It turned to a French distributor, Gaches Chimie, for a third oil, Rhodorsil 47V1000.

Brenntag confirmed it sold silicone oils to PIP from 2001 to 2010, but said it stopped when it was made aware PIP was under investigation. A Brenntag spokesman,

Hubertus Spethmann, said that as far as Brenntag knew, PIP was a diversified supplier whose products included wound dressing pads and other padding products that could be filled with silicones such as the oils it produced. Brenntag would not comment on the orders PIP made or any payment problems with the French company.

Reuters could not independently confirm that these items were sold by PIP.

Representatives from Brenntag periodically asked to visit PIP's headquarters, according to one ex-PIP employee, a request that caused much worry within PIP. Brenntag would not comment on the visits.

On at least two occasions, Brenntag sales representatives paid a visit, but were welcomed by Mas in his office and did not visit the production labs, the former worker said this month.

"Mas would tell them we used the silicone oil for creams, certainly not breast implants," said the ex-worker. "We were very uncomfortable and let Mas do all the talking."

Gaches Chimie also confirmed it occasionally sold its silicone oil to PIP from the early 2000s until 2009, when the orders stopped. CEO Pierre Gaches said he did not believe his company was PIP's main supplier and never had concerns about the ultimate use of the oil, because it is used in many industrial applications.

NEW BMWS

Even as PIP used unapproved materials for its silicone implants, its innovative saline products were running into problems in the United States. Lawsuits from hundreds of patients alleged they deflated, sometimes within months of surgery. The FDA was never to approve PIP's silicone products, instead posting a warning about the firm's practices on its website.

Mas made a reverse takeover to try to open PIP to U.S. capital and prepare the way for a re-launch.

In 2003, his Luxembourg holding company Milo Finance bought a majority stake in U.S.-listed Heritage Worldwide, and handed to Heritage the control of PIP. In its first annual filing with the U.S. Securities and Exchange Commission after the merger, Heritage disclosed that for the financial year ended June 23, 2003, PIP had a loss of $693,336. That loss grew to $5.6 million in 2004.

PIP also turned to markets where regulation was not as stringent. It found distributors to open sales in 10 new countries "in which no regulatory problems were anticipated," Heritage said in its 2003 annual report. Exports were less profitable - foreign sales fetched about a third of the French price - but there was volume in South America, which soon became PIP's top market with two-thirds of sales, driven by Venezuela and Colombia.

In 2005 and 2006, PIP showed a profit. One former employee said these were the "glory days" for the company, which employed about 120 workers. Operating margins reached 20 percent, the sort of level an early cellphone maker could expect.

"We'd see a smile on the face of Mr. Couty," said a former manager. One of those years, the company bought new BMWs for Couty and Mas, Couty told police. He did not respond to requests for an interview.

Mas, now at France's retirement age of 65, took on a chairman's "supervisory and advice-giving" role in 2004, for which he received 360,000 euros per year, a five-fold rise over his 2003 salary.

Finance chief Couty became CEO, but PIP's liquidator, Xavier Huertas, wrote in a March 2010 report that Mas continued to control production, R&D and sales, and "in fact, to lead the company at the side of Mr. Couty."

However, crisis was around the corner. Litigation and the financial shocks of 2008 were to send Mas back into PIP's labs, to try to improve on his "perfect" gel formula.

FRICTION MOUNTS

Mas was never trained as a scientist. He was a tinkerer, an experimenter who relied on his gut. But even he was to realise that PIP gel had a problem: it leaked too much silicone oil.

Of seven former PIP staff interviewed by Reuters, only two said they had no idea that the company was using a homemade gel. Three others suggested they kept quiet because they were worried about their jobs.

After 2005, PIP staff became more vocal. That year, the heads of production, quality control and research and development together asked Mas to fill all PIP's implants with NuSil, Hannelore Font, the company's quality control director, told police. Mas replied this would be "economically impossible". Font did not return calls requesting an interview.

For 2008, PIP set aside 1.4 million euros to cover potential lawsuits, according to liquidation documents. It had underestimated. A British court ordered the company to pay 1.6 million euros to plaintiffs who alleged the envelopes covering PIP's implants were not strong enough and leaked gel. U.S. litigation cost another 160,000 euros.

"All this litigation weakened the health of the company," said Haddad, the attorney for PIP and Mas.

REUTERS/JEAN-PAUL PELISSIER

WRECKAGE: Nearly two years after PIP was shut down by regulators, squatters have defecated on the floor of its former offices, while boxes of implants strew the company's abandoned building near Toulon

Complaints rose, and PIP's customers paid more slowly. The liquidator noted that PIP's export clients on average took nearly nine months to settle.

Suppliers balked, too. NuSil held up a shipment destined for PIP due to non-payment, PIP's purchasing manager, Nadine Carrodano, told police. Couty wrote to Mas describing what he called his "fears for the future."

By June 30, 2009, PIP's debts reached 8.5 million euros. "In every area the company was crumbling," Carrodano told police. She declined to comment.

"FINGER IN THE GEL"

In 2008, PIP invested 300,000 euros on a new machine to make the implants' shells, hoping more uniformity would cut leakage, according to Couty.

Brinon, PIP's technical director, said Mas came to him in early 2008 and told him to start developing a new gel, PIP 2. Brinon refused, and the task went instead to another worker who had never worked on implants before coming to PIP. The goal, he said, was to create a gel that would not leak so much oil. This was crucial: silicone gel that seeps out may cause irritation and inflammation in women's bodies.

That worker told Reuters that Mas relied on trial and error, adding a bit of this and a bit of that in the lab: "He didn't do scientific tests," the former worker said. "He'd look and say, 'that's good, that's bad.'"

To judge whether more or less oil was seeping out of the gel, the worker said, "you would look and then put your finger in the gel

and you'd see if there was oil or not on your finger."

Finally, midway through 2008, PIP 2 was ready.

Brinon was sceptical. His own mother, who had once had cancer, had a PIP implant and he was worried, he told police. He began doing his own tests on PIP gel and NuSil. He told police that PIP 1 gel excreted more oil than PIP 2, and much more than NuSil, which leaked oil in "infinitessimal amounts."

A FINAL THUMBS-UP

Mas threw himself into export sales. His passport, a copy of which is included in police documents, shows visits to Panama, Venezuela, Colombia, Brazil, Uruguay, Ecuador, China, Singapore and the Philippines in 2008 and 2009.

Back at home, staff morale was low.

On May 4, 2009, a commerce court in the city of Toulon ordered PIP into the French equivalent of Chapter 11 proceedings.

About a dozen employees were laid off, month-to-month workers' contracts were cut and evening shifts scaled back, according to liquidation documents.

Font, the quality-control staffer, told police she delivered an ultimatum to Mas at a meeting with other managers, saying she would no longer sign off on implants ready to be shipped. Instead, Couty took that on.

TUV performed an audit in early 2010. Purchasing manager Carrodano told police she was "close to tears" after TUV gave PIP the thumbs-up. Font got a doctor to sign a medical release to keep her away from work. Unpaid suppliers stopped sending raw materials; production ground to a halt.

"FRAGILE PEOPLE"

On March 16, 2010, AFSSAPS officials came calling, a visit that had been arranged five days in advance. AFSSAPS had recently received letters from a Marseille surgeon signalling his concerns with PIP rupture rates. The regulator also received in the mail photos sent anonymously of empty containers of non-approved raw materials at PIP's plant.

On the first day of their visit, inspectors noticed nothing abnormal. The following morning, without telling PIP, they visited PIP's production facility. It was then they spotted the empty containers labeled "Silop,"

REUTERS/JEAN-PAUL PELISSIER

VACANT LOT: The gates to PIP's former production site in La Seyne-sur-Mer have been welded shut following the factory's closure

for Silopren. The lead inspector estimated they had contained nearly 9 tonnes of the liquid silicone.

Days later, when police visited the site, Mas slipped out quickly. When French police finally managed to question him in November, they asked why he had left in such a hurry. According to a police transcript of the interview, he said he was no longer in charge of the company - he had handed the reins to his finance director years back. "I thought it wasn't me you were coming to see..."

Within two weeks of the regulators' visit, PIP was shut down and AFSSAPS pulled its implants from the market. Some 29,000 products were seized. Laid-off staff burned tyres and hurled discarded implants into the car park.

Mas went abroad again. Costa Rica, Nicaragua, Columbia, Spain and Venezuela are among visits his passport records in 2010. In Costa Rica, he was pulled over and charged with drunk driving.

On Sept. 27, 2010, Mas transferred his ownership of a real estate holding company to his partner Lucciardi and their son, according to Luxembourg filing documents. That company holds the title to a four-bedroom villa with a pool not far from PIP's headquarters.

It was here police arrested Mas in January. The home, according to estate agents, is currently listed for sale at about 1.6 million euros.

In their questioning of Mas in October 2011, he told police that over the years, 75 percent of PIP's implants were filled with his homemade formula. The French regulator says there are so far 1,262 cases of the devices rupturing in France. Health experts say no concrete link has been shown between PIP implants and breast cancer, but the French government has advised women to have their PIP implants removed.

Mas, who is out on bail, was asked by police what he thought of the women who issued complaints about the failed devices.

"It's about fragile people, or people who are doing it for the money," he said, according to the interview transcript.

(Alexandria Sage reported from Paris, Natalie Huet from La-Seyne-sur-Mer and Jean-Francois Rosnoblet from Marseille; additional reporting by Marc Joanny in La-Seyne-sur-Mer, Elena Berton in Paris, and Ludwig Burger and Maria Sheahan in Frankfurt; writing by Alexandria Sage; Editing by Sara Ledwith and Simon Robinson)

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