

# Composition and toxicity of PIP silicone

Current MHRA view: November 4<sup>th</sup> 2012

## Introduction

One aim of the MHRA has been to determine whether, and to what extent, PIP breast implant silicone represents a risk to human health.

In pursuing this, two questions have been addressed:

- Does the chemical composition of PIP silicone differ from medical grade silicone used in approved breast implants?
- Does PIP silicone have potential health hazards not associated with medical grade silicone?

## Chemical composition of PIP breast implant silicone

MHRA commissioned LGC to perform analytical work. For this purpose 5 samples of PIP breast implants and 6 batches of medical grade breast implants were studied. The PIP breast implants provided for analysis were selected to represent a range of batch numbers and expiry dates.

LGC used FTIR (Fourier Transform Infrared Spectroscopy), GC-MS (Gas Chromatography Mass Spectrometry) and ICP-MS (Inductively Coupled Plasma Mass Spectrometry).

The key findings were as follows:

### *Organic*

- There was no evidence in any implant for any significant organic impurities
- Compared with medical grade silicone, PIP silicone displayed significantly increased levels of low molecular weight siloxanes
- There were no other differences between PIP silicone and medical grade silicone
- There were no differences in the composition of individual batches of PIP silicone (other than in the levels of siloxanes)

### *Inorganic*

- There were no significant inorganic impurities in any batch of silicone implant
- There were no major differences between any of the batches tested
- A low level of caesium (0.3 ppm) was found in PIP silicone, but not in medical grade silicone
- Platinum levels were found to be lower in PIP silicone (0.1ppm) than in medical grade silicone (3ppm)

The conclusions that can be drawn from this are:

- *PIP batches do not display batch to batch variation with respect to chemical composition, other than with regard to levels of siloxanes*
- *The only potentially biologically relevant differences between PIP silicone and medical grade silicone is that in the former there are increased levels of siloxanes*

These data are consistent with comparable analyses conducted by Agence Francaise de Securite Sanitaire des Produits de Sante (AFSSAPS; the French regulatory authority), and by the Australian Therapeutic Goods Administration (TGA).

### **Toxicity testing of PIP silicone**

There is information available regarding genotoxicity, cytotoxicity and skin irritation from studies commissioned previously. These are summarised as follows:

#### *Genotoxicity*

Studies commissioned by the MHRA and AFSSAPS in 2010 revealed that PIP silicone lacked genotoxic potential.

#### *Cytotoxicity*

Testing by AFSSAPS in 2010 showed the absence of cellular cytotoxicity. More recently cytotoxicity tests commissioned by TGA have yielded the same negative result.

#### *Skin irritation*

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

More recently the TGA commissioned two separate studies, one performed in Australia and a second in Europe. In both instances all batches of test material, including organic and aqueous extracts of PIP silicone and PIP implant shells, were uniformly negative. The conclusion drawn at that time, based on all the data available, was that silicone from PIP breast implants lacked the potential to cause skin irritation.

Since then, in 2012, the MHRA commissioned additional studies on the ability of silicone from batches of PIP breast implants to cause genotoxicity, cellular cytotoxicity and skin irritation. These assessments were all conducted using well-established and fully validated *in vitro* test methods. Five different batches of PIP breast implant (and 1 control implant of medical grade) were selected for analysis, and in each case both aqueous and organic extracts of implant silicone were tested.

In all tests both aqueous and organic extracts of all batches of implant silicone were uniformly negative.

These data provide additional confirmatory evidence that silicone derived from PIP breast implants is non-genotoxic and lacks the potential to cause either cellular cytotoxicity or skin irritation.

## Toxicity of siloxanes

The programme of testing summarised above failed to disclose any toxic properties of silicone derived from PIP breast implants. It is nevertheless appropriate to consider the toxicity of siloxanes and whether their increased concentrations in PIP implant silicone represents a health risk.

The most common, and the most thoroughly investigated, siloxanes are:

*Octamethylcyclotetrasiloxane (D4)*

*Decamethylcyclopentasiloxane (D5)*

*Dodecamethylcyclohexasiloxane (D6)*

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

- Siloxanes are not genotoxic
- It is generally accepted that these materials exhibit low acute toxicity following exposure by oral, dermal or inhalation administration
- They fail to cause skin or eye irritation
- They do not cause allergic sensitisation

One issue that needs to be addressed derives from a review of D4 by the SCCP (Scientific Committee on Consumer Products) dated 2005. In that review it was reported that inhalation exposure of rats to D4 was associated with delayed ovulation associated with reduced fertility. The No Observable Adverse Effect Level (NOAEL) was judged to be 300ppm by inhalation. On that basis siloxane D4 is identified under the CLP (Classification, Labelling and Packaging) regulations as having adverse effects on fertility.

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

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

Moreover, in 2010 the Scientific Committee for Consumer Safety (SCCS) published this opinion:

*“The SCCS is of the opinion that cyclomethicone (D4, D5) does not pose a risk for human health when used in cosmetics”*

### **Siloxanes risk assessment**

To date the only hazard of potential concern has been evidence from rodent studies of effects on female fertility. However, the opinion of the SCCP was that this does not represent a risk to human health.

It is nevertheless appropriate to consider the concentrations of siloxanes D4, D5 and D6 in PIP implants, and in medical grade implants, should formal risk assessments be required in the light of emerging data.

Some information about the levels of individual siloxanes D4, D5 and D6 in PIP breast implants has been provided by the LGC, as follows:

<b>Siloxane</b>	<b>Concentration (<math>\mu\text{g/g}</math>) median and (range)</b>
D4	180 (40-270)
D5	210 (0-640)
D6	170 (10-710)

The analyses revealed that the levels of D4, D5 and D6 found in extracts of PIP implants represented only a minor proportion of the total amount of siloxane species present.

In 2 batches of medical grade silicone that were analysed in the same way the data were as follows:

<b>Siloxane</b>	<b>Concentration (<math>\mu\text{g/g}</math>) sample 1/sample 2</b>
D4	20/50
D5	10/10
D6	20/10

It should also be appreciated that that the method used for extraction was not validated, and there is some uncertainty about the absolute concentrations of siloxanes D4, D5 and D6.

It is appropriate to compare these data with similar analyses of PIP breast implants reported in March 2012 by the TGA. Those results were as follows:

<b>Siloxane</b>	<b>Concentration (ppm) median and (range)</b>
D4	136 (0-261)
D5	434 (0-710)
D6	474 (0-1005)

The units reported by LGC ( $\mu\text{g/g}$ ) are equivalent to ppm used in the TGA study, so the results are broadly comparable with regard to the concentrations of D4, D5 and D6.

In the TGA report it was claimed that the results they obtained were generally consistent with those reported by AFSSAPS. Moreover, information provided to TGA by suppliers of the raw materials that were used to produce the gel used in PIP breast implants suggests that the above values provide a reasonable estimate of the levels of D4, D5 and D6 siloxanes.

AFSSAPS has reported that NUSIL silicone contained less than 50ppm low molecular mass silicones, and that is consistent with the results obtained by LGC using 2 batches of medical grade silicone.

Finally, it must be acknowledged that the siloxanes that have been the subject of most thorough examination (D4, D5 and D6) represented only a minor fraction of the total siloxane content of PIP breast implants analysed by the LGC. There is little or no information about such siloxanes, but there is no reason to suspect that they represent any greater health risk than do the D4, D5 and D6 species.

## Overview and Current Position

On the basis of currently available information:

- PIP silicone is not genotoxic or cytotoxic, and does not cause skin irritation
  - There is no evidence for variation between batches of PIP with regard to chemical composition, other than with respect to levels of siloxanes
  - PIP silicone does not contain any major organic or inorganic impurities
  - PIP silicone contains significantly higher concentrations of siloxanes (10-fold or greater) than does medical grade silicone
  - Siloxanes are not genotoxic, do not cause skin or eye irritation, fail to cause allergic sensitisation, and do not display acute toxicity
  - Siloxane D4 has been found to cause reduced female fertility in rats following inhalation exposure to concentrations of 300ppm or greater. However, this is not regarded as representing a risk to human health.
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- **PIP breast implant silicone differs from medical grade silicone only with respect to an increased concentration of siloxanes. This is not believed to represent a risk to human health.** This conclusion is consistent with the views of the TGA as reported in March 2012: *“The results of the TGA testing for these small silicone molecules (siloxanes) confirms the results obtained by the French authorities, but the presence of these chemicals (which are widely used in cosmetics) is not considered a health risk”*.